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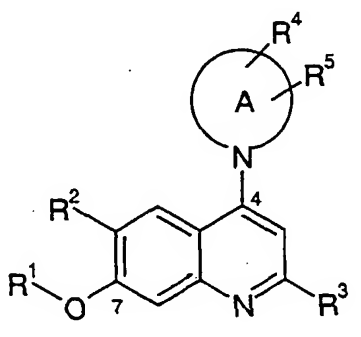
(54) Title: QUINOLINE DERIVATIVES AS LIGANDS FOR THE NEUROPEPTIDE Y RECEPTOR



(I)

(57) Abstract: Compounds of formula (I) as well as pharmaceutically acceptable salts and esters thereof, wherein R^1, R^2, R^3, R^4, R^5 and A have the significance given in claim 1, can be used in the form of pharmaceutical preparations for the treatment or prevention of arthritis, cardiovascular diseases, diabetes, renal failure, eating disorders and obesity.

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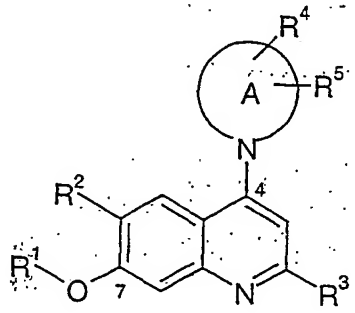
QUINOLINE DERIVATIVES AS LIGANDS FOR THE NEUROPEPTIDE Y RECEPTOR

The present invention is concerned with novel quinoline derivatives useful as neuropeptide Y (NPY) receptor ligands, particularly neuropeptide Y (NPY) antagonists.

The invention is concerned especially with compounds of formula I



I

and pharmaceutically acceptable salts and esters thereof, wherein

R^1 is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH_2-SO_2-, monoalkylamino-SO_2-, dialkylamino-SO_2-, alkyl-SO_2-, aryl, NH_2-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, aryl-SO_2-O-alkyl, cycloalkyl or cycloalkylalkyl;

R^2 is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino,

heteroarylamino, NH_2-, monoalkylamino, dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, aryl, arylalkoxy or heteroarylalkoxy;

R^3 is hydrogen, alkyl, NH_2-, monoalkylamino, dialkylamino or alkoxy;

R^4 is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, NH_2-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO_2- or aryl-SO_2-;

R^5 is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, NH_2-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO_2- or aryl-SO_2-; and

A is a 5- to 10- membered mono- or bicyclic saturated heterocyclic ring comprising the nitrogen atom which is attached to the quinoline ring and optionally one or two further heteroatoms which are independently selected from oxygen, sulfur and nitrogen.

The compounds of formula I and their pharmaceutically usable salts and are novel and have valuable pharmacological properties. They are neuropeptide ligands, for example neuropeptide receptor antagonists and in particular, they are selective neuropeptides Y Y5 receptor antagonists.

Neuropetide Y is a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems. This peptide mediates a number of physiological effects through its various receptor subtypes. Studies in animals have shown that neuropeptide Y is a powerful stimulus of food intake, and it has been demonstrated that activation of neuropeptide Y Y5 receptors results in hyperphagia and decreased thermogenesis. Therefore compounds that antagonise neuropetide Y at the Y5 receptor subtype represent an approach to the treatment of eating disorders such as obesity and hyperphagia.

The current approach is aiming at medical intervention to induce weight loss or prevention of weight gain. This is achieved by interfering with appetite control, which is mediated by the Hypothalamus, an important brain region proven to control food intake. Herein, neuropeptide Y (NPY) has been proven to be one of the strongest central

mediators of food intake in several animal species. Increased NPY levels result in profound food intake. Various receptors of neuropeptide Y (NPY) have been described to play a role in appetite control and weight gain. Interference with these receptors is likely to reduce appetite and consequently weight gain. Reduction and long-term maintenance of body weight can also have beneficial consequences on con associated risk factors such as arthritis, cardiovascular diseases, diabetes and renal failure.

Accordingly, the compounds of formula I can be used in the prophylaxis or treatment of of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

Objects of the present invention are the compounds of formula I and their aforementioned salts and esters per se and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically usable salts and esters, the use of the said compounds, esters and salts for the prophylaxis and/or therapy of illnesses, especially in the treatment or prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders such as hyperphagia and particularly obesity, and the use of the said compounds, salts and esters for the production of medicaments for the treatment or prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1 to 6 carbon atoms and particularly preferred a straight or branched-chain alkyl group with 1 to 4 carbon atoms Examples of straight-chain and branched C_1-C_8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl and ethyl and most preferred methyl.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C_3-C_8 cycloalkyl are cyclopropyl, methyl-cyclopropyl, dimethylcyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, methyl-cyclohexyl, dimethyl-cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl.

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy,

ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec. butoxy and tert.butoxy, 2-hydroxyethoxy, 2-methoxyethoxypreferably methoxy and ethoxy and most preferred methoxy.

The term "aryloxy", alone or in combination, signifies a group of the formula aryl-O- in which the term "aryl" has the previously given significance, such as phenyloxy.

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group, preferably a phenyl group which optionally carries one or more substituents each independently selected from halogen, trifluoromethyl, amino, alkyl, alkoxy, alkylcarbonyl, cyano, carbamoyl, alkoxycarbamoyl, methylendioxy, carboxy, alkoxycarbonyl, aminocarbonyl, alkyaminocarbonyl, dialkylaminocarbonyl, hydroxy, nitro and the like, such as phenyl, chlorophenyl, trifluoromethylphenyl, chlorofluorophenyl, aminophenyl, methylcarbonylphenyl, methoxyphenyl, methylendioxyphenyl, 1-naphthyl and 2-naphthyl. Preferred is phenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 3-aminophenyl, 4-methylcarbonylphenyl, 4-methoxyphenyl and particularly phenyl.

The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred are benzyl, benzyl substituted with hydroxy, alkoxy or halogen, preferably fluorine. Particularly preferred is benzyl.

The term "heterocyclyl", alone or in combination, signifies a saturated, partially unsaturated or aromatic 4- to 10-membered heterocycle which contains one or more, preferably one ore two hetero atoms selected from nitrogen, oxygen and sulfur, wherein oxygen and particularly nitrogen are preferred. If desired, it can be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, cyano, haloalkyl preferably trifluoromethyl and heterocyclyl, preferably morpholinyl and pyrrolidinyl, and/or on a secondary nitrogen atom (i.e. -NH-) by alkyl, cycloalkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e.=N-) by oxido, with halogen, alkyl, cycloalkyl and alkoxy being preferred. The term "heterocyclyl" also includes the term heteroaryl. Examples of heterocyclyl groups are pyridinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 3,4-dihydro-1H-isoquinolinyl, azepanyl, tetrahydrofuranyl and thiophenyl, wherein each of these rings can be substituted by one or more, preferably one or two substituents independently selected from alkyl, alkoxy, halogen, trifluoromethyl, cyano, morpholinyl and pyrrolidinyl. Particularly preferred examples of heterocycly are pyridinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiophenyl, tetrahydrofuranyl and furyl, wherein each of these rings is optionally substituted with one or more, preferably one or

two substituents selected from alkyl, alkoxy, halogen, trifluoromethyl, cyano, morpholinyl and pyrrolidinyl.

The term "heteroaryl", alone or in combination, signifies aromatic 5- to 10-membered heterocycle which contains one or more, preferably one or two hetero atoms selected from nitrogen, oxygen and sulfur, wherein nitrogen or oxygen are preferred. If desired, it can be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, cyano, haloalkyl, heterocyclyl, preferably trifluoromethyl. Preferred heteroaryl cycles are pyridinyl or thiophenyl optionaly substituted by one or more, preferably one or two substituents independently selected from halogen, alkyl, alkoxy, cyano, haloalkyl, preferably trifluoromethyl, and heterocyclyl, preferably morpholinyl or pyrrolidinyl.

The term "amino", alone or in combination, signifies a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group carrying an alkyl or cycloalkyl substituent and the tertiary amino group carrying two similar or different alkyl or cycloalkyl substituents or the two nitrogen substitutents together forming a ring, such as, for example, $-NH_2$, methylamino, ethylamino, dimethylamino, diethylamino, methyl-ethylamino, pyrrolidin-1-yl or piperidino etc., preferably amino, dimethylamino and diethylamino and particularly primary amino.

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably fluorine, chlorine or bromine.

The term "alkenyl", alone or in combination signifies a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms. Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and isobutenyl.

The term "alkinyl", alone or in combination signifies a straight-chain or branched hydrocarbon residue comprising a carbon carbon triple bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms. Examples of alkinyl groups are ethinyl, 1-propinyl, 2-propinyl, 1-butinyl, 2-butinyl and 3-butinyl.

The term "carboxy", alone or in combination signifies the -COOH group.

The term "carboxyalkyl", alone or in combination signifies an alkyl group as defined before, wherein one or more, preferably one hydrogen atom is replaced by a carboxy group. An example is carboxymethyl.

The term "hydroxyalkyl", alone or in combination signifies an alkyl group as define before, wherein one or more, preferably one hydrogen atom is replaced by a hydroxy group.

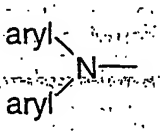
The term "aryloxy", alone or in combination signifies the group aryl-O- , wherein the term aryl is defined as before.

The term "cyano", alone or in combination signifies the group -CN.

The term "heterocyclyloxy", alone or in combination signifies the group heterocyclyl-O- , wherein the term heterocyclyl is defined as before.

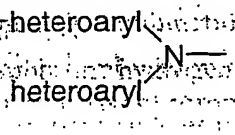
The term "actetylamino", alone or in combination signifies the group -NH-CO-CH_3.

The term "arylamino", alone or in combination signifies the group aryl-NH- or



wherein the term aryl is defined as before and, wherein both aryl groups are the same or are different.

The term "heteroarylamino", alone or in combination signifies the group heteroaryl-NH- or



wherein the term heteroaryl is defined as before and, wherein both heteroaryl groups are the same or are different.

The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, preferably hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxylic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the

like. In addition these salts may be prepared form addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polymine resins and the like. The compound of formula I can also be present in the form of zwitterions. Particularly preferred pharmaceutically acceptable salts of compounds of formula I are the hydrochloride salts.

The compounds of formula I can also be solvated, e.g. hydrated. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration). The term pharmaceutically acceptable salts also includes physiologically usable solvates.

"Pharmaceutically acceptable esters" means that compounds of general formula (I) may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo. Examples of such compounds include physiologically acceptable and metabolically labile ester derivatives, such as methoxymethyl esters, methylthiomethyl esters and pivaloyloxymethyl esters. Additionally, any physiologically acceptable equivalents of the compounds of general formula (I), similar to the metabolically labile esters, which are capable of producing the parent compounds of general formula (I) in vivo, are within the scope of this invention.

The term "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, 1994). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterized in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to orlistat.

Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

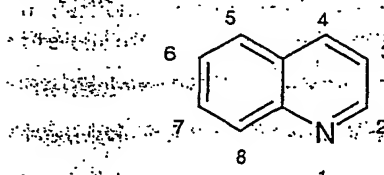
Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the lipase inhibitor be administered within about one or two hours of ingestion of a meal containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity and has obtained a body mass index of 25 or greater.

Orlistat can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, other sugars and sugar alcohols like sorbitol, mannitol, maltodextrin, or other fillers; surfactants like sodium lauryle sulfate, Brij 96, or Tween 80; disintegrants like sodium starch glycolate, maize starch or derivatives thereof, polymers like povidone, crospovidone; talc; stearic acid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents and antioxidants. They can also contain still other therapeutically valuable substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art. Preferably, orlistat is administered according to the formulation shown in the Examples and in U.S. Patent No. 6,004,996, respectively.

The compounds of formula I can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for

example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

In the nomenclature used in the present description the ring atoms of the quinoline ring are numbered as follows:



Preferred are compounds of the formula I, wherein

R^1 is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH_2-SO_2-, monoalkylamino-SO_2-, dialkylamino-SO_2- or alkyl-SO_2-;

R^2 is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH_2-, mono- or dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, aryl, heteroaryl, arylalkoxy or heteroarylalkoxy;

R^3 is hydrogen, alkyl, NH_2-, monoalkylamino, dialkylamino or alkoxy;

R^4 is hydrogen, alkyl, alkoxy, hydroxy, NH_2-, monoalkylamino, dialkylamino, acetylamino or cyano;

R^5 is hydrogen;

A is a saturated ring consisting of a nitrogen atom which is attched to the quinoline ring and a $-(CH_2)_n$- moiety with n being 4, 5, or 6;

and pharmaceutically acceptable salts and esters thereof.

Preferred compounds of formula I are those, wherein R^1 is hydrogen, alkyl, alkenyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, dialkylamino-SO_2-, alkyl-SO_2-, dialkylaminoalkyl, alkoxycarbonylalkyl, aryl-SO_2-O-alkyl or cycloalkylalkyl.

In a further preferred embodiment of the invention R^1 is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH_2-, mono- or dialkylamino-SO_2-, or alkyl-SO_2-. A further preferred embodiment of the present invention R^1 is hydrogen, cycloalkylalkyl, aralkyl, or heteroarylalkyl. Further

preferred are compounds according to formula (I), wherein R^1 is hydrogen, aralkyl or heteroarylalkyl. Particularly preferred are compounds of formula (I), wherein R^1 is hydrogen, phenylalkyl or pyridinylalkyl wherein the phenyl- and the pyridinyl cyles are optionally substituted with one to three substituents independently selected from the group consisting of alkyl, alkoxy, cyano, or halogen, preferably, methyl, alkoxy, cyano, or halogen. Further particularly preferred are compounds, wherein R^1 is hydrogen, cyclopropylmethyl, (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl, pyridinylmethyl, (fluropyridinyl)methyl, (chloropyridinyl)methyl, or (methylpyridinyl)methyl. Very preferred are compounds, wherein R^1 is hydrogen, cyclopropylmethyl, (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl or pyridinylmethyl. Particularly preferred are compounds of formula I, wherein R^1 is hydrogen, cyclopropylmethyl, (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl, pyridinylmethyl, chloropyridinylmethyl or fluoropyridinylmethyl.

In a preferred emodiment of the present invention R^2 is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH_2-, mono- or dialkylamino or aryl(alkyl)amino. In another preferred embodiment of the invention R^2 is hydrogen, alkyl, or halogen. Particularly preferred are compounds of formula (I), wherein R^2 is hydrogen. Likewise preferred are compounds according to formula (I), wherein R^2 is alkyl. Other preferred compounds of formula (I) are those, wherein R^2 is hydrogen, butyl, fluoro, chloro or bromo. Particularly preferred are hydrogen, butyl, fluoro or bromo.

A preferred aspect of the present invention are compounds according to formula I, wherein R^3 is hydrogen, alkyl, aralkoxy, heteroarylalkoxy, NH_2- , mono- or di-alkylamino. Further preferred compounds of formula (I) are those, wherein R^3 is hydrogen, alkyl, or NH_2- . Preferred compounds are those, wherein R^3 is alkyl, particularly methyl.

Preferred are compounds of formula I, wherein R^4 is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, monoalkylamino, dialkylamino, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, heterocyclylalkyl or alkyl-SO_2-.

In a preferred embodiment of the invention R^4 is hydrogen, alkyl or alkoxy. Another preferred aspect of the present invention are compounds of formula (I), wherein R^4 is hydrogen or alkoxy. Particularly preferred compounds of formula I are those, wherein R^4 is hydrogen, alkoxy, alkoxyalkyl, hydroxyalkyl or hydroxy. Very preferred is hydrogen.

Further preferred are those compounds of formula I, wherein A is a 5- to 10-membered mono- or bicyclic saturated heterocyclic ring comprising the nitrogen atom which is attached to the quinoline ring and optionally one or two further oxygen atoms. Preferred compounds according to formula I are those, wherein A is pyrrolidinyl, azepanyl, morpholinyl, 1,4-dioxa-8-aza-spiro(4.5)dec-8-yl or piperidinyl.

Other preferred compounds of formula (I) are those, wherein A is a pyrrolidinyl or azepanyl ring. Particularly preferred is a pyrrolidinyl ring.

Preferred compounds of formula I are those, wherein R^5 is hydrogen.

Examples of preferred compounds of formula (I) are

1. 7-Benzyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
2. 2-Methyl-4-pyrrolidin-1-yl-quinolin-7-ol;
3. Dimethyl-sulfamic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester;
4. Methanesulfonic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester;
5. 7-Cyclopropylmethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
6. 7-(3-Methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
7. 7-Methoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
8. 2-Methyl-7-(pyridin-2-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
9. 7-Allyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
10. 7-Isobutoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
11. 7-(2-Methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
12. 2-Methyl-4-pyrrolidin-1-yl-7-(tetrahydro-furan-2-ylmethoxy)-quinoline;
13. 7-(4-Methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
14. 2-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
15. 4-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
16. 2-Methyl-4-pyrrolidin-1-yl-7-(2-trifluoromethyl-benzyloxy)-quinoline;

17. 2-Methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-benzyloxy)-quinoline;

18. 2-Methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-benzyloxy)-quinoline;

19. 7-(2-Chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

20. 7-(3-Chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

21. 7-(4-Chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

22. 2-Methyl-7-(pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

23. 3-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

24. 7-Isopropoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;

25. 7-(2-Methoxy-ethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

26. 2-Methyl-7-(2-morpholin-4-yl-ethoxy)-4-pyrrolidin-1-yl-quinoline;

27. 2-Methyl-7-(pyridin-4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

28. (S)-7-Benzyloxy-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;

29. (S)-4-(3-Ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;

30. (S)-4-(3-Ethoxy-pyrrolidin-1-yl)-7-(3-methoxy-benzyloxy)-2-methyl-quinoline;

31. (S)-4-[4-(3-Ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

32. (S)-2-[4-(3-Ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

33. 7-Benzyloxy-6-butyl-4-pyrrolidin-1-yl-quinoline;

34. 6-Butyl-4-pyrrolidin-1-yl-quinolin-7-ol;

35. 6-Butyl-7-methoxy-4-pyrrolidin-1-yl-quinoline;

36. 6-Butyl-7-ethoxy-4-pyrrolidin-1-yl-quinoline;

37. 6-Butyl-7-cyclopropylmethoxy-4-pyrrolidin-1-yl-quinoline;

38. 4-(6-Butyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

39. 4-Azepan-1-yl-7-benzyloxy-2-methyl-quinoline;

40. 4-Azepan-1-yl-2-methyl-quinolin-7-ol;

41. 4-Azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline;

42. 4-(4-Azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;

43. 3-(4-Azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;

44. 4-Azepan-1-yl-2-methyl-7-(pyridin-2-ylmethoxy)-quinoline;

45. 6-Bromo-7-methoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;

46. 6-Bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol;

47. 4-(6-Bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

48. 7-Methoxy-4-pyrrolidin-1-yl-quinolin-2-ylamine;

49. 7-Methoxy-4-pyrrolidin-1-yl-quinoline;

50. 4-Pyrrolidin-1-yl-quinolin-7-ol;

51. 7-(3,5-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

52. 7-(3,4-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

53. 7-ethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;

54. 2-Methyl-7-(6-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

55. 2-methyl-7-(2-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

56. 7-(6-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

57. 7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

58. 7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

59. 7-(2-chloro-6-methyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

60. 7-(2-chloro-6-trifluoromethyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

61. 5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-pyridine-2-carbonitrile;

62. 7-(5-chloro-thiophen-2-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

63. 2-methyl-4-pyrrolidin-1-yl-7-(thiophen-3-ylmethoxy)-quinoline;

64. 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-benzonitrile;

65. (S) 4-(3-ethoxy-pyrrolidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinoline;

66. (S) 7-(2-chloro-pyridin-3-ylmethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;

67. (S) 4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-7-(pyridin-3-ylmethoxy)-quinoline;

68. (S) 5-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile;

69. 4-azepan-1-yl-7-(3-methoxy-benzyloxy)-2-methyl-quinoline;

70. 2-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;

71. 4-azepan-1-yl-7-(3-chloro-benzyloxy)-2-methyl-quinoline;

72. 4-Azepan-1-yl-7-(4-chloro-benzyloxy)-2-methyl-quinoline;

73. 2-methyl-7-(6-morpholin-4-yl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

74. 2-methyl-4-pyrrolidin-1-yl-7-(6-pyrrolidin-1-yl-pyridin-3-ylmethoxy)-quinoline;

75. [2,2-dimethyl-3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-propyl]-dimethyl-amine;

76. 2-methyl-7-(1-methyl-piperidin-4-yloxy)-4-pyrrolidin-1-yl-quinoline;

77. 2-methyl-4-pyrrolidin-1-yl-7-(tetrahydro-furan-3-yloxy)-quinoline;

78. 2-Methyl-7-(1-methyl-piperidin-4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

79. 2-methyl-7-(3-morpholin-4-yl-propoxy)-4-pyrrolidin-1-yl-quinoline;

80. (2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-acetic acid ethyl ester;

81. 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethanol;

82. toluene-4-sulfonic acid 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethyl ester;

83. 2-methyl-7-(3-pyridin-2-yl-propoxy)-4-pyrrolidin-1-yl-quinoline;

84. 7-benzyloxy-2-methyl-4-morpholin-4-yl-quinoline;

85. (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol;

86. (R)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol;

87. (S)-[1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol;

88. (S)-7-benzyloxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

89. (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;

90. (S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

91. (S)-7-(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

92. (S)- 7-cyclopropylmethoxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

93. (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;

94. (S)- {1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;

95. (S)- {1-[7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;

96. (S)- 2-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

97. (S)- {1-[2-methyl-7-(pyridin-3-ylmethoxy)-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;

98. (S)- 5-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile;

99. 7-benzyloxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;

100. 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol;

101. 4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

102. 6-fuoro-2-methyl-7-(pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

103. 6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

104. 7-(2-chloro-pyridin-3-ylmethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;

105. 6-fluoro-2-methyl-7-(2-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;

106. 3-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

107. 2-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

108. 7-cyclopropylmethoxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;

109. 5-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-pyridine-2-carbonitrile;

110. (R)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline;

111. (S)-7-benzyloxy-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinoline;

112. (S)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline;

113. (S)-7-benzyloxy-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;

114. (S)-7-benzyloxy-4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinoline;

115. 7-benzyloxy-2-methyl-4-{(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinoline;

116. (S)- 4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol;

117. (S)- 4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;

118. (S)- 4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;

119. (S)- 4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol;

120. 2-methyl-4-{(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinolin-7-ol;

121. (S)- 4-{4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile;

122. (S)- 4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

123. (S)-4-[4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

124. (S)-4-{4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile;

125. (S)-4-{4-[3-(2-Hydroxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile;

126. (S)-[1-(7-benzyloxy-6-fluoro-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol;

127. (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;

128. (S)-4-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

129. (S)-5-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile;

130. (S)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

131. (R)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

132. (R,S)-4-[2-methyl-4-(2-methyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

133. (S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

134. (R)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

135. (R)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

136. (S)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

137. (R)-4-[4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

138. (S)-4-[4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

139. (R,S)-4-[4-(2-isopropyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

140. (S)-1-[7-(4-cyano-benzyloxy)-2-methyl-quinolin-4-yl]-pyrrolidine-2-carboxylic acid methyl ester;

141. (R)- 4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

142. (S)- 4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

143. 4-(2-methyl-4-piperidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

144. 4-(2-methyl-4-morpholin-4-yl-quinolin-7-yloxymethyl)-benzonitrile;

145. (R,S)-4-[4-(3-diethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

146. (R,S)-4-[2-methyl-4-(3-pyridin-2-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

147. (R,S)-4-[2-methyl-4-(3-pyridin-4-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

148. (S)- 4-[2-methyl-4-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

149. (R,S)-4-[4-(3-methanesulfonyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

150. (R,S)-4-[2-methyl-4-(3-methyl-piperidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

151. 4-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile and

152. (R,S)- 4-[4-(3-hydroxymethyl-piperidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile.

Examples of particularly preferred compounds of formula (I) are

2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol;

7-(3-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

7-(3-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(4-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

(S)-4-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol;

4-(6-butyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

4-azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline;

4-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;

3-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;

7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

(S) 4-(3-ethoxy-pyrrolidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinoline;

(S) 7-(2-chloro-pyridin-3-ylmethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;

(S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

(S)-7-(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

(S)- {1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;

(S)- {1-[7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;

4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(2-chloro-pyridin-3-ylmethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;

(S)- 4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

(S)-4-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

(S)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

(R)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

(S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile and

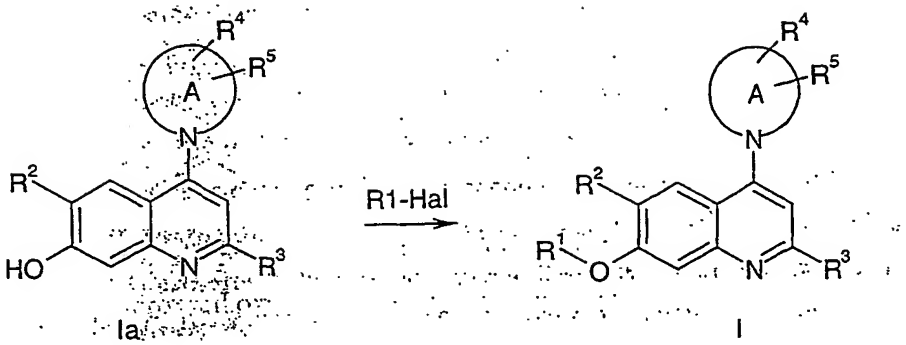
(R)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile.

Processes for the manufacture of compounds of formula I are an object of the invention.

The substituents and indices used in the following description of the processes have the significance given above unless indicated to the contrary.

Compounds of general formula I can be obtained according to scheme 1 from compounds of formula Ia comprising R^2 substituents according to the above definition by an alkylation reaction with, e.g. K_2CO_3 as a base and in a suited solvent such as DMF. The alkylation reaction to introduce R^1 can also be performed on the intermediates described below, prior to implementation of the substituents in 4-quinoline poition by inverting the reaction steps.

Scheme 1



Alternatively, compounds of formula I can be obtained from Ib, according to scheme 2, by an alkylation reaction as above to give compounds of formula 1c and subsequent Pd catalysed C/O, C/N or C/C bond forming reactions in analogy to known procedures. Thus, substituted alkoxy, and amino groups can be introduced via a C/O, C/N bond forming reaction under Buchwald conditions, from the corresponding alkohols and amines with, for example, $Pd(OAc)_2$ as catalyst, BINAP (2,2-bis(dipenylphosphino)-1,1-binaphthyl) as chelating phosphine ligand and with NaOtBu as a base - in a solvent such as toluene and at elevated temperature (S. L. Buchwald in: J Am. Chem. Soc. 1996, p. 10333 and Acc. Chem Res. 1998, p 805 for the general method).

With repect to Pd catalysed C/C bond forming methods to introduce the above defined substituted alkyl and (hetero)aryl groups: This can be achieved via Suzuki-type coupling (for aryl, heteroaryl substitutents) starting from well described or commercial aryl or heteroaryl boronic acids with, for example, $Pd(PPh_3)_4$ as catalyst, Na_2CO_3 as base, in DMF at elevated temperature (general method: Synth. Commun. 1991, p 513). An alternative consists in using the correponding aryl or heteroaryl stannanes in a Stille-type coupling (for general method: Ang. Chem IE, 1986, 508).

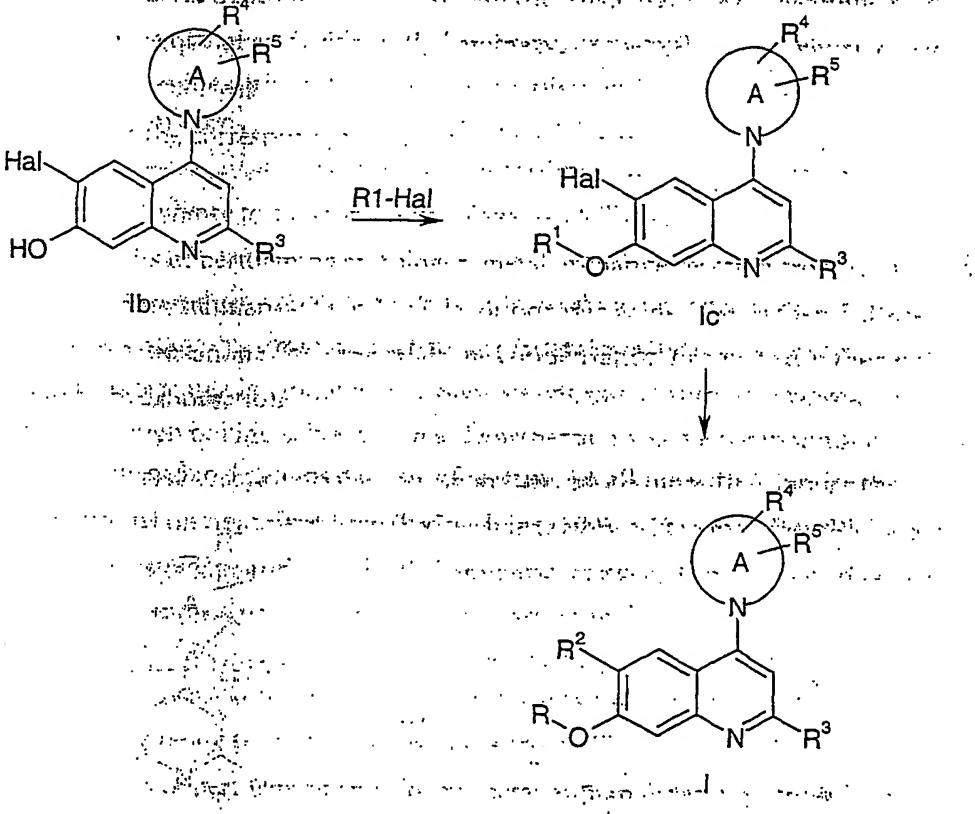
Procedures to introduce arylalky, heteroarylalkyl consists of applying the reaction discussed above or to use Pd catalysed C/C bond formation under Negishi conditions, starting from the known arylalkyl, heteroarylalkyl Li or Mg salts, with $Pd(PPh_3)_4$ as catalyst, in the presence of $ZnCl_2$ and in THF as solvent (general method: Acc. Chem. Res. 1982, p340). Other methods (e.g for arylethyl, heteroarylethyl group introduction) consists of performing a Heck-type coupling, starting from a correponding (hetero)aryl olefine and 1c, with $Pd_2(dba)_3$ as catalyst, $P(t\text{-}Bu)_3$ as phosphine ligand, $CsCO_3$ as base in DMF as

solvent at elevated temperature. (G.C. Fu in: J. Org. Chem. 1999, p. 10 for recent application of the reaction). The (hetero)arylalkene condensation products can then be reduced further by hydrogenation.

A method to introduce alkinyl groups consists of reacting an alkine with Ic under the Sonogashira conditions (review: Org. Prep. Proceed. Int. 1995, p127) with $Pd(PPh_3)_4$ as catalyst, in the presence of CuI and with triethyl amine as a base. Alkenyl dervivatives are obtained from alkenes via Heck coupling as pointed out above, and alkyl as R^2 substituent can be obtained from the corresponding alkenes by hydrogenation.

An alternative sequence to perform above discussed Stille-, Negishi and Suzuki-type condensations consisits of performing an halogen/metal exchange reaction from Ic , to obtain the correponding stannanes, Li or Mg salts or boronic acids. This is then followed by a Pd-catalysed condensation with appropriate halogenides (R^2Hal) according to the general methods given above.

Scheme 2

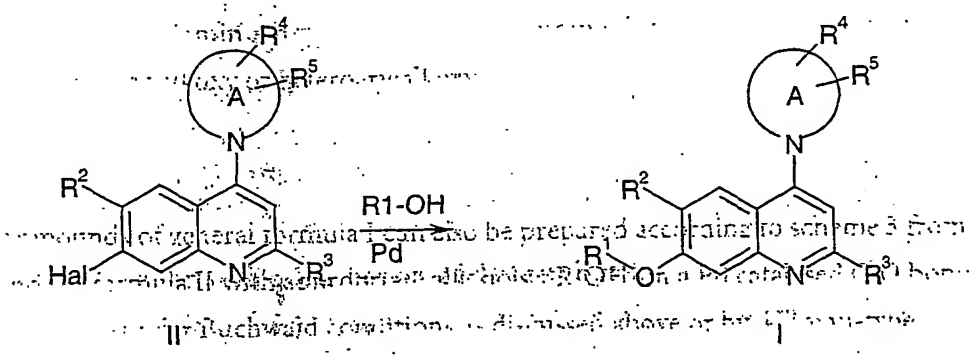


R^2 is halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH_2-,

mono- or dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, aryl, heteroaryl, arylalkoxy or heteroarylalkoxy.

Compounds of general formula I can also be prepared according to scheme 3 from compounds of formula II with appropriate alkohols (R^1OH) in a Pd catalysed C/O bond forming reaction under Buchwald conditions as discussed above or by Ullman-type rection with, for example CuCl, in a solvent such as DMF, in analogy to a method described by J.A. Ragan: Synthesis 1998, p1599.

Scheme 3

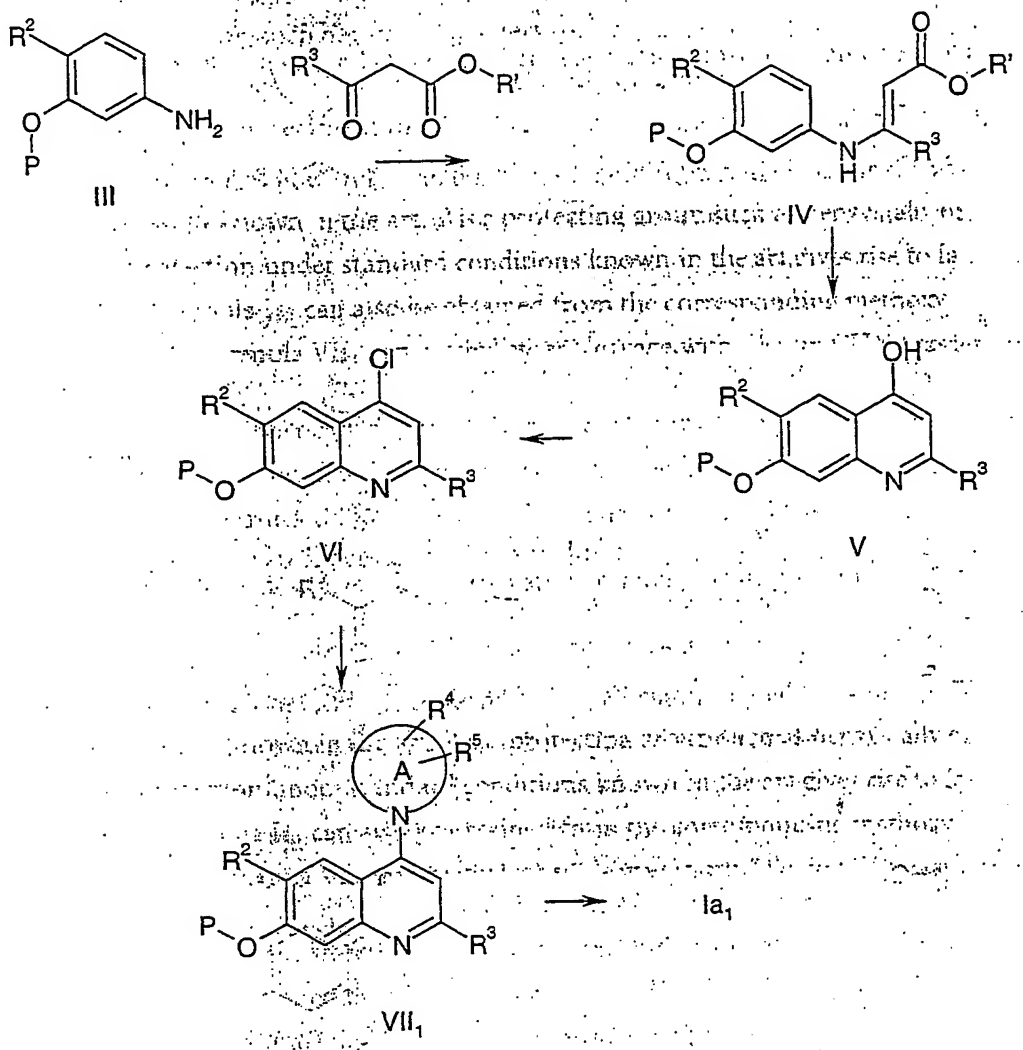


Compounds of general formula Ia, b and II can be prepared as follows:

The preparation of compounds according to formula Ia_1, wherein R^3 is not $-NH_2$-, alkylamino, dialkylamino or alkoxy, is achieved is according to scheme 4, starting from appropriate anilines which are either known in the literature or which can being prepared by standard procedures known in the art. Thus, condensation with corresponding alkoxycarbonyl ketones or aldehydes in the presence of p-toluenesulfonic acid, in refluxing cyclohexane and under capture of water produced during the reaction, the enamine derivatives of general formula IV are obtained. Subsequent ring closure is achieved, on heating at 250 °C in a high boiling solvent such as Dowtherm A to give compounds of general formula V. Transformation to the corresponding chloro quinoline derivatives of formula VI is performed on treatment with $POCl_3$ under reflux, a standard method known in the literature. Subsequent reaction with corresponding amines as defined above, either using a large excess of amine without solvent or on reaction with a 2-fold access, in a suited solvent such as ethanol or THF and in the presence of catalytic amounts of NaI and with pyridine as a base, gives compounds of formula VII_1. The amines used are either substituted with R^4, R^5 groups as defined or the groups can be introduced by functional

group conversion as known in the art. P is a protecting group such as benzyl, ally or tert.butyl. Deprotection under standard conditions known in the art gives rise to Ia_1. Compounds of formula Ia_1 can also be obtained from the corresponding methoxy derivatives (P=Me, formula VII_1) on methyl ether cleavage with BBr_3 in CH_2Cl_2 as a solvent.

Scheme 4



R^3 is hydrogen or alkyl;

P is a protecting group such as e.g. benzyl, allyl or tert.butyl;

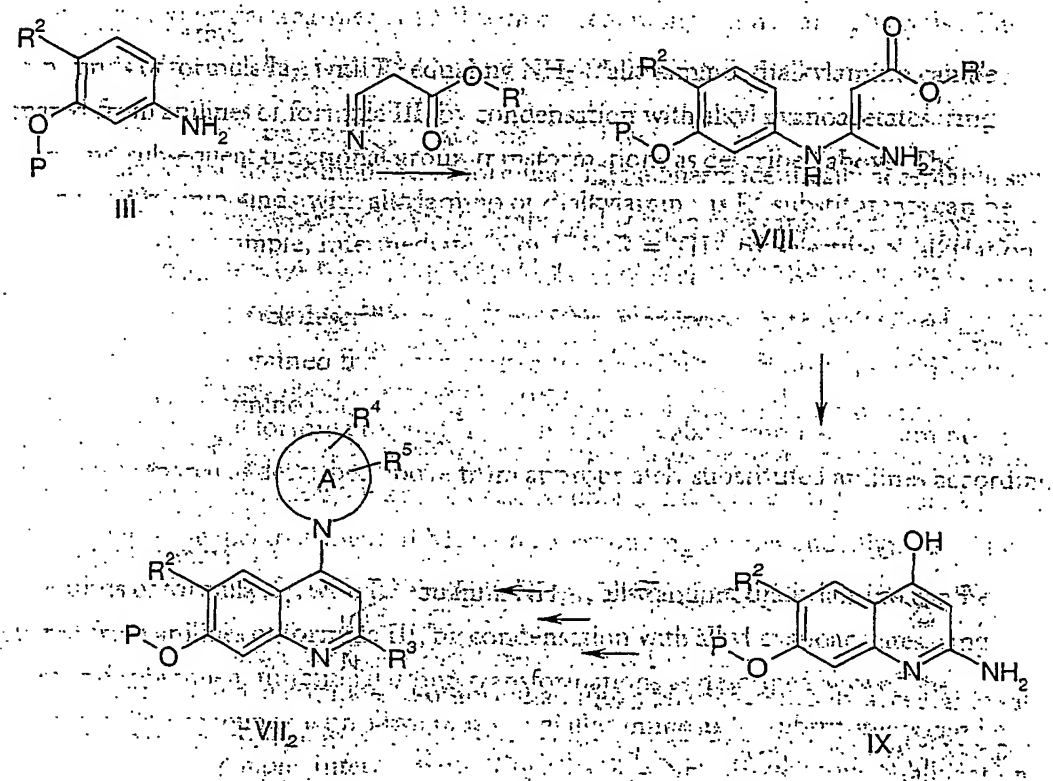
R' is methyl or ethyl.

Compounds of general formula Ib_1 and II_1 (R^3 not NH_2- , alkylamino, dialkylamino or alkoxy) are prepared as described above from appropriately substituted anilines according to scheme 4.

Compounds of formula Ia_2, with R^3 equaling NH_2- , alkylamino, dialkylamino can be prepared from anilines of formula III, by condensation with alkyl cyanoacetates, ring closure and subsequent functional group transformations as described above. The corresponding compounds with alkylamino or dialkylamino as R^3 substitutents can be obtained from, for example, intermediate IX or VII_2 ($R^3 = NH_2$) by selective N-alkylation.

In analogy to the sequence described in scheme 5 and starting from the appropriate anilines there can be obtained the compounds of fomula Ib_2 and II_2 (R^3 equaling NH_2- or alkylamino or dialkylamino).

Scheme 5



R^3 is NH_2- , alkylamino or dialkylamino;

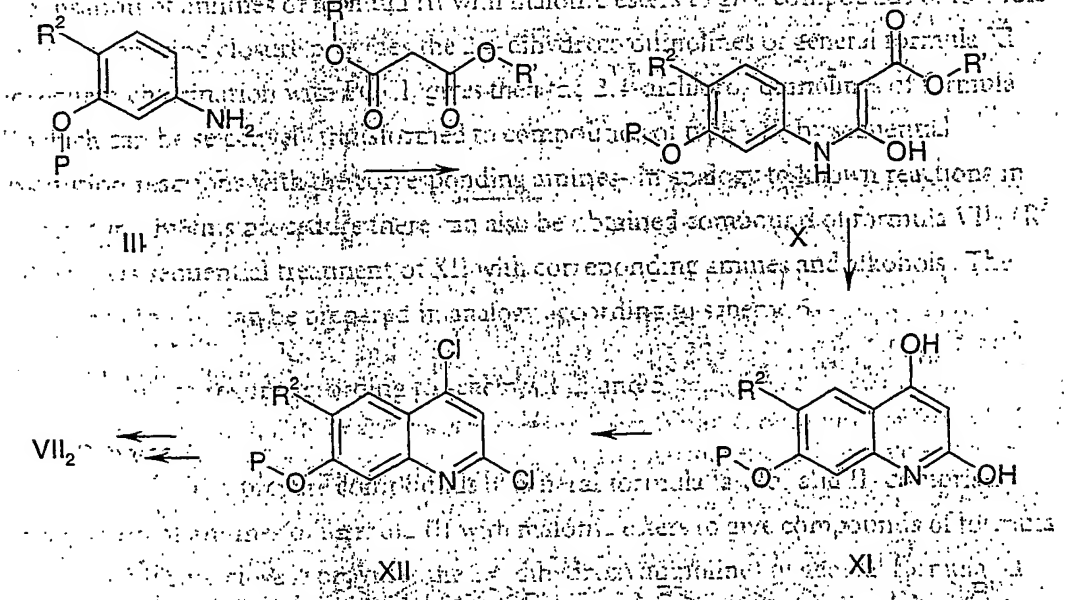
R' is methyl or ethyl;

P is a protecting group such benzyl, allyl or tert.-butyl.

A further method to prepare compounds of general formula Ia_2, Ib_2 and II_2 comprises condensation of anilines of formula III with malonic esters to give compounds of formula X. Subsequent ring closure provides the 2,4-dihydroxyquinolines of general formula XI. Subsequent chlorination with $POCl_3$ gives then the 2,4-dichloro- quinolines of formula XII which can be selectively transformed to compounds of type VII_2 by sequential substitution reactions with the corresponding amines- in analogy to known reactions in the literature. By this procedure there can also be obtained compound of formula VII_2 (R^3 is alkoxy) via sequential treatment of XII with correponding amines and alkohols . The compounds Ib_2, II_2 can be prepared in analogy according to scheme 6.

Preferred procedures are according to schemes 1, 2 and 5.

Scheme 6



R^3 is NH_2-, alkylamino, dialkyl amino or alkoxy;

R' is methyl or ethyl;

R" is methyl or ethyl.

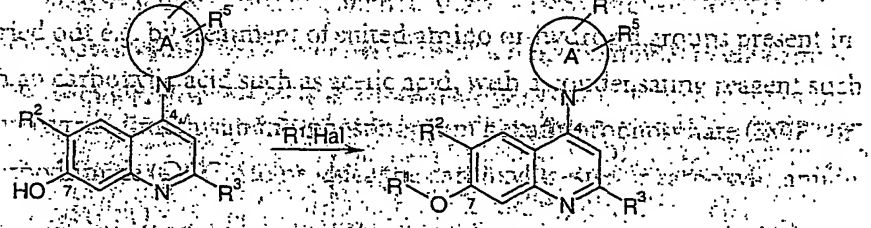
The conversion of a compound of formula I into a pharmaceutically acceptable salt can be carried out by treatment of such a compound with an inorganic acid, for example a hydrohalic acid, such as, for example, hydrochloric acid or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid etc., or with an organic acid, such as, for example, acetic

acid, citric acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. The corresponding carboxylate salts can also be prepared from the compounds of formula I by treatment with physiologically compatible bases.

The conversion of compounds of formula I into pharmaceutically usable esters or amides can be carried out e.g. by treatment of suited amino or hydroxyl groups present in the molecules with an carboxylic acid such as acetic acid, with a condensating reagent such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) or N,N-dicylohexylcarbodiimide (DCCI) to produce the carboxylic ester or carboxylic amide.

A preferred process for the preparation of a compound of formula I comprises one of the following reactions:

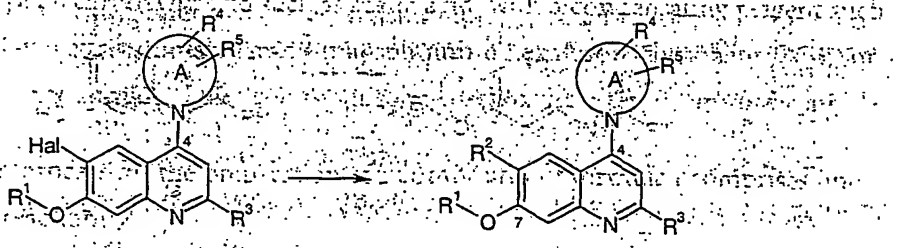
a) reaction of a compound of the formula Ia in the presence of a compound of the formula R^1-Hal



Ia I

wherein R^1, R^2, R^3, R^4, R^5 and A are as defined before and Hal is halogen; or

b) Pd catalyzed C/O, C/N or C/C bond forming reaction of a compound of formula Ic in order to obtain a compound of formula I



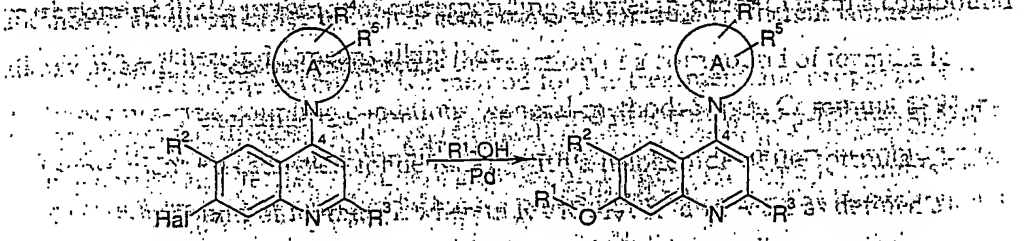
Ic I

wherein R^1, R^2, R^3, R^4, R^5 and A are defined as before and Hal is halogen, preferably chloro, bromo or iodo. Preferred is the reaction of a compound according to

formula Ic under Buchwald conditions (S. L. Buchwald in: J Am. Chem. Soc. 1996, p. 10333 and Acc. Chem Res. 1998, p.805 for the general method), particularly in the presence of $Pd(OAc)_2$, BINAP and a base such as NaOtBu with a corresponding alkohol or amine in order to form a compound of formula I, wherein R^2 means alkoxy or amino. Further preferred is the reaction of a compound of formula Ic under Suzuki-type coupling conditions (general method: Synth. Commun. 1991, p 513) in the presence of corresponding arylboronic acids or heteroarylboronic acids in order to form a compound of formula I, wherein R^2 means aryl or heteroaryl. Also preferred is the reaction of a compound of formula Ic under Stille coupling conditions (for general method: Ang. Chem IE, 1986, 508) in the presence of corresponding arylstannanes or heteroarylstannanes in order to form a compound of formula I, wherein R^2 means aryl or heteroaryl. Further preferred is the reaction of a compound of formula Ic under Sonogashira conditions (review: Org. Prep. Proceed. Int. 1995, p127), particularly in the presence of CuI and a base such as triethylamine in the presence of corresponding alkines in order to form a compound of formula I, wherein R^2 means alkinyl; or

c) a halogen/metal exchange reaction of a compound of formula Ic as defined in step b) and subsequent Pd catalyzed condensation with a halogenide of the formula R^2-Hal to yield a compound of formula I, wherein R^1, R^3, R^4, R^5 and A are as defined as before, Hal is halogen and R^2 is alkenyl, alkinyl, alkoxy, alkoxyalkoxy, aryloxy, arylamino, heteroarylamino, NH_2-, monoalkylamino, dialkylamino, arylalkylamino, heteroarylalkylamino, aryl, arylalkoxy or heteroarylalkoxy; or

d) reaction of a compound of formula II in the presence of an alcohol of the formula R^1-OH and a palladium catalyst in order to obtain a compound of formula I



II

wherein R^2, R^3, R^4, R^5 and A are defined as before, Hal is halogen and R^1 is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH_2-SO_2-, monoalkylamino-SO_2-, dialkylamino-SO_2-, alkyl-SO_2-,

aryl, NH_2-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, aryl-SO_2-O-alkyl, cycloalkyl or cycloalkylalkyl.

A particularly preferred process for the preparation of a compound of formula I comprises one of the reactions a), c) or d) as mentioned before.

Preferred intermediates are:

7-benzyloxy-4-chloro-2-methyl-quinoline;

7-benzyloxy-6-butyl-4-chloro-quinoline hydrochloride;

6-bromo-4-chloro-7-methoxy-2-methyl-quinoline.

The compounds of formula I described above for use as therapeutically active substances are a further object of the invention.

Also an object of the invention are compounds described above for the production of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the NPY receptor, particularly for the production of medicaments for the prophylaxis and therapy of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

Likewise an object of the invention are pharmaceutical compositions containing a compound of formula I described above and a therapeutically inert carrier.

An object of the invention is also the use of the compounds described above for the production of medicaments, particularly for the treatment and prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

A further object of the invention comprises compounds which are manufactured according to one of the described processes.

A further object of the invention is a method for the treatment and prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity whereby an effective amount of a compound described above is administered.

According to a further aspect of the invention there is provided a method of treatment of obesity in a human in need of such treatment which comprises

administration to the human a therapeutically effective amount of a compound according to formula I and a therapeutically effective amount of a lipase inhibitor, particularly preferred, wherein the lipase inhibitor is orlistat. Also subject of the present invention is the mentioned method, wherein the administration is simultaneous, separate or sequential.

A further preferred embodiment of the present invention is the use of a compound of the formula I in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor, particularly preferred, wherein the lipase inhibitor is orlistat.

Assay Procedures

Cloning of mouse NPY5 receptor cDNAs:

The full-length cDNA encoding the mouse NPY5 (mNPY5) receptor was amplified from mouse brain cDNA using specific primers, designed based on the published sequence, and Pfu DNA-Polymerase (Stratagene). The amplification product was subcloned into the mammalian expression vector pcDNA3 using Eco RI and XhoI restriction sites. Positive clones were sequenced and one clone, encoding the published sequence was selected for generation of stable cell clones.

Stable transfection:

Human embryonic kidney 293 (HEK293) cells were transfected with 10 µg mNPY5 DNA using the lipofectamine reagent (Gibco BRL) according to the manufacturer's instruction. Two days after transfection, geneticin selection (1 mg/ml) was initiated and several stable clones were isolated. One clone was further used for pharmacological characterization.

Radioligand competition binding:

Human embryonic kidney 293 cells (HEK293), expressing recombinant mouse NPY5-receptor (mNPY5) were broken by three freeze/thawing cycles in hypotonic Tris

buffer (5 mM, pH 7.4, 1 mM $MgCl_2$), homogenized and centrifuged at 72,000 x g for 15 min. The pellet was washed twice with 75 mM Tris buffer, pH 7.4, containing 25 mM $MgCl_2$ and 250 mM sucrose, 0.1 mM phenylmethylsulfonylfluoride and 0.1 mM 1,10-pheneanthrolin, resuspended in the same buffer and stored in aliquots at -80°C. Protein was determined according to the method of Lowry using bovine serum albumine (BSA) as a standard.

Radioligand competition binding assays were performed in 250 µl 25 mM Hepes buffer (pH 7.4, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 1 % bovine serum albumine, and 0.01 % NaN_3 containing 5 µg protein, 100 pM [^{125}I]labelled peptide YY (PYY) and 10 µL DMSO containing increasing amounts of unlabelled test compounds. After incubation for 1 h at 22°C, bound and free ligand are separated by filtration over glass fibre filters. Non specific binding is assessed in the presence of 1 µM unlabelled PYY. Specific binding is defined as the difference between total binding and non specific binding. IC_{50} values are defined as the concentration of antagonist that displaces 50 % of the binding of [^{125}I]labelled neuropeptide Y. It is determined by linear regression analysis after logit/log transformation of the binding data.

Results obtained in the foregoing test using representative compounds of the invention as the test compounds are shown in the following table:

Compound	NPY5-R (mouse) IC_{50} (nM)
7-cyclopropylmethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline (example 5)	27
6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol (example 34)	9.9

Preferred compounds as described above have IC_{50} values below 1000 nM; more preferred compounds have IC_{50} values below 100 nM, particularly below 10 nM. Most preferred compounds have IC_{50} values below 2 nM. These results have been obtained by using the foregoing test.

The compounds of formula I and their pharmaceutically usable salts and esters can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula I and their pharmaceutically usable salts and esters can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

In accordance with the invention the compounds of formula I and their pharmaceutically usable salts can be used for the prophylaxis and treatment of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and

obesity. The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should be appropriate. It will, however, be clear that the upper limit given above can be exceeded when this is shown to be indicated.

The invention is illustrated hereinafter by Examples, which have no limiting character.

Examples

Example 1

a) A mixture of 534 mg (1.8 mmol) of 7-benzyloxy-4-chloro-2-methyl-quinoline and 3.77 ml (45 mmol) pyrrolidine was heated at 80°C (oil bath temperature) under an argon atmosphere for 23 h after which time the reaction was completed according to HPLC analysis. The reaction was partitioned between EtOAc and water, the aqueous layer was extracted once with EtOAc, the combined organic layers were washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was applied to silica gel column with CH_2Cl_2/MeOH/NH_4OH (19:1: 0.05) as eluent. Combination of the purified fractions and concentration in vacuo gave 430 mg (74.5%) of the 7-benzyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline as a brown solid. ISP mass spectrum, m/e: 319.4 (M+1 calculated for $C_{21}H_{22}N_2O$: 319).

Preparation of the starting material:

b) 20 g (98.4 mmol) of 3-benyloxyaniline, 12.6 ml (0.984 mmol) of ethyl acetoacetate and 0.189 g (1 mmol) of p-toluenesulfonic acid monohydrate in 32 ml of cyclohexane were heated at reflux for 5.5 h in the presence of a water-separator funnel. The reaction mixture was cooled to RT, some solid material was filtered off by suction and the filtrate was concentrated in vacuo to give 30.6 g (99%) of the desired 3-(3-benzyloxy-phenylamino)-but-2-enoic acid ethyl ester as a yellow oil. This was used without further purification in the next reaction step.

c) 3.67 g (11.8 mmol) of 3-(3-benzyloxy-phenylamino)-but-2-enoic acid ethyl ester were added dropwise within 20 minutes to 5.5 ml of Dowtherm A heated at 250°C (metal bath temperature). The solution was stirred further 10 minutes at 250°C (bath temperature), cooled to RT and then treated with 20 ml of heptane. The brown viscous oil that had formed was isolated and triturated with 45 ml of AcOEt. The brown solid obtained was filtered off by suction, washed with AcOEt and dried in a high vacuum to give 1.19 g (35%) of 7-benzyloxy-2-methyl-quinolin-4-ol. ISP mass spectrum, m/e: 266.3 (M+1 calculated for $C_{17}H_{15}NO_2$: 266).

d) 1.15 g (3.99 mmol) of 7-benzyloxy-2-methyl-quinolin-4-ol in 7.46 ml (79.8 mmol) of $POCl_3$ were heated at 130°C (oil bath temperature) for 1h 40 min until completion of the

reaction according to TLC analysis. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was taken up in ice water and stirred for 2 h. The pH was adjusted to values between pH 9-10 with concentrated NH_4Cl, the brown solid which precipitated was filtered off by suction, washed with water and subsequently dried in a high vacuum. This gave 1 g (84.5%) of 7-benzyloxy-4-chloro-2-methyl-quinoline as a brown solid. EI mass spectrum, m/e: 283.1 (M+1 calculated for $C_{17}H_{14}ClNO$: 283).

Example 2

A solution of 13 g of 7-benzyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline, product of example 1, dissolved in 750 ml of MeOH was treated with 4 g of palladium on charcoal (10%) and then hydrogenated at RT for 1.5 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, washed with water, and the solution was concentrated in vacuo. The solid that precipitated was collected by filtration and dried in a high vacuum to give 8.9 g (96.2%) of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol as an amorphous yellow solid. ISP mass spectrum, m/e: 229.2 (M+1 calculated for $C_{14}H_{16}N_2O$: 229).

Example 3

229.4 mg (1mmol) of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, were suspended under an argon atmosphere in 20 ml of DMF, 0.6 g (1.2mmol) of molecular sieves (4nm) were added followed by 138 mg (1.2 mmol) of potassium tert-butoxide, and the mixture was stirred for 1 h at RT. It was then cooled to 0°C, treated with 0.13 ml (1.2 mmol) N,N-dimethylsulfamoylchloride and stirred for 3 h at 0°C. The reaction mixture was partitioned between EtOAc and water, the aqueous layer was extracted twice with EtOAc, the combined organic layers were washed with water, then with saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was triturated with diethyl ether; the viscous oil obtained was filtered off by suction and dried in a high vacuum. Upon further triturating with heptane solid material was obtained which was dried in a high vacuum to give 100 mg (29.3%) of dimethyl-sulfamic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester as an off-white solid. ISP-mass spectrum, m/e: 336.2 (M+1 calculated for $C_{16}H_{21}N_3O_3S$: 336).

Example 4

In analogy to example 3, from 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, and methanesulfonyl chloride there was obtained methanesulfonic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester as an off-white solid. ISP mass spectrum, m/e: 307.3 (M+1 calculated for $C_{15}H_{18}N_2O_3S$: 307).

Example 5

In analogy to example 3, from 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, and cyclopropylmethyl bromide - with reaction times of 19 h (0°C) and isolation of the product as hydrochloride, via treatment of the reaction product with HCl-saturated diethyl ether - there was obtained 7-cyclopropylmethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 283.2 (M+1 calculated for $C_{18}H_{22}N_2O$: 283).

Example 6

A mixture of 114 mg (0.5 mmol) of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, 166 mg (0.6 mmol) of potassium carbonate and 84 µl (0.6 mmol) of 3-methoxybenzyl chloride was heated at 80°C in 8 ml of DMF under an argon atmosphere for 23 h. The mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was separated, washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was taken up in diethyl ether and some not dissolved material was removed by filtration. The filtrate was treated under stirring with 0.25 ml of 3N HCL in MeOH and stirring was continued for 1h. The solid that precipitated was filtered off by suction and dried in a high vacuum to give 138 mg (69.7%) of 7-(3-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as an light-yellow solid. ISP mass spectrum, m/e: 349.4 (M+1 calculated for $C_{22}H_{24}N_2O_2$: 349).

Example 7

In analogy to example 6 there was prepared, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with methyl iodide, 7-methoxy-2-methyl-4-pyrrolidin-1-yl-quinoline

hydrochloride as an off-white solid. ISP mass spectrum, m/e: 243.3 (M+1 calculated for $C_{15}H_{18}N_2O$: 243).

Example 8

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-picolyl chloride, whereby the product was isolated as free base, 2-methyl-7-(pyridin-2-ylmethoxy)-4-pyrrolidin-1-yl-quinoline as a light brown solid. ISP mass spectrum, m/e: 320.4 (M+1 calculated for $C_{20}H_{21}N_3O$: 320).

Example 9

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with allyl bromide, whereby the product was isolated as free base, 7-allyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline as a light yellow solid. EI mass spectrum, m/e: 268.2 (M calculated for $C_{17}H_{20}N_2O$: 268).

Example 10

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with isobutyl bromide, 7-isobutoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 285.3 (M+1 calculated for $C_{18}H_{24}N_2O$: 285).

Example 11

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-methoxybenzyl chloride, 7-(2-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 349.4 (M+1 calculated for $C_{22}H_{24}N_2O_2$: 349).

Example 12

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with tetrahydro-furfuryl bromide, whereby the product was isolated as free base, (rac) 2-methyl-4-pyrrolidin-1-yl-7-(tetrahydro-furan-2-ylmethoxy)-quinoline as a yellow-brown waxy solid. ISP mass spectrum, m/e: 313.2 (M+1 calculated for $C_{19}H_{24}N_2O_2$: 313).

Example 13

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with of 4-methoxybenzyl chloride, 7-(4-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-yellow solid. ISP mass spectrum, m/e: 349.4 (M+1 calculated for $C_{22}H_{24}N_2O_2$: 349).

Example 14

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-bromomethyl benzonitrile, whereby the product was isolated as free base, 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a brown solid. ISP mass spectrum, m/e: 344.4 (M+1 calculated for $C_{22}H_{21}N_3O$: 344).

Example 15

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-bromomethyl-benzonitrile whereby the product was isolated as free base, 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a brown solid. ISP mass spectrum, m/e: 344.4 (M+1 calculated for $C_{22}H_{21}N_3O$: 344).

Example 16

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-(trifluoromethyl)-benzyl chloride, 2-methyl-4-pyrrolidin-1-yl-7-(2-

trifluoromethyl-benzyloxy)-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 387.4 (M+1 calculated for $C_{22}H_{21}F_3N_2O_2$: 387).

Example 17

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with of 3-(trifluoromethyl)-benzyl chloride, 2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-benzyloxy)-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 387.4 (M+1 calculated for $C_{22}H_{21}F_3N_2O_2$: 387).

Example 18

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with of 4-(trifluoromethyl)-benzyl chloride, 2-methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-benzyloxy)-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 387.4 (M+1 calculated for $C_{22}H_{21}F_3N_2O_2$: 387).

Example 19

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-chlorobenzyl chloride, 7-(2-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 353.3 (M+1 calculated for $C_{21}H_{21}ClN_2O$: 353).

Example 20

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-chlorobenzyl chloride, 7-(3-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-yellow solid. ISP mass spectrum, m/e: 353.3 (M+1 calculated for $C_{21}H_{21}ClN_2O$: 353).

Example 21

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-chlorobenzyl chloride, 7-(4-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 353.3 (M+1 calculated for $C_{21}H_{21}ClN_2O$: 353).

Example 22

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-(chloromethyl)pyridine hydrochloride, whereby the product was isolated as free base, 2-methyl-7-(pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline as a red solid. ISP mass spectrum, m/e: 320.4 (M+1 calculated for $C_{22}H_{21}N_3O$: 320).

Example 23

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-bromomethyl benzonitrile, whereby the product was isolated as free base, 3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a yellow solid. ISP mass spectrum, m/e: 344.4 (M+1 calculated for $C_{22}H_{21}N_3O$: 344).

Example 24

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-bromopropane, 7-isopropoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-yellow solid. ISP mass spectrum, m/e: 271.4 (M+1 calculated for $C_{17}H_{22}N_2O$: 271).

Example 25

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 1-bromo-2-methoxyethane, 7-(2-methoxy-ethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-brown solid. ISP mass spectrum, m/e: 287.2 (M+1 calculated for $C_{17}H_{22}N_2O_2$: 287).

Example 26

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-(2-chloroethyl)-morpholine hydrochloride, whereby the product was isolated as free base, 2-methyl-7-(2-morpholin-4-yl-ethoxy)-4-pyrrolidin-1-yl-quinoline as a brown solid. ISP mass spectrum, m/e: 342.3 (M+1 calculated for $C_{20}H_{27}N_3O_2$: 342).

Example 27

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-(chloromethyl)pyridine hydrochloride, 2-methyl-7-(pyridin-4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-yellow solid. ISP mass spectrum, m/e: 320.4 (M+1 calculated for $C_{20}H_{21}N_3O$: 320).

Example 28

a) A mixture of 436 mg (1.5 mmol) of 7-Benzyloxy-4-chloro-2-methyl-quinoline, product of example 1d), and 1.75 g (15 mmol) of (S)-3-ethoxypyrrolidine, prepared according to Tetrahedron Lett., 1995, 2745, was heated at 80°C (oil bath temperature) under an argon atmosphere for 18 h after which time the reaction was completed according to HPLC analysis. The excess (S)-3-ethoxy-pyrrolidine was distilled off, and the residue was partitioned between EtOAc and water. The layers were separated, the organic layer was washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was taken-up in MeOH (1ml) diluted with diethyl ether (30 ml) and then treated dropwise at RT under stirring with 0.7 ml of 3N HCL in MeOH. The solvent was removed and the remaining salt triturated with diethyl ether, then filtered off by suction and dried in a high vacuum to give 425 mg (69.7%) of the (S)-7-benzyloxy-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 363.2 (M+1 calculated for $C_{23}H_{26}N_2O_2$: 363).

Example 29

A solution of 93 mg (0.23 mmol) of (S)-7-Benzyloxy-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride, product of example 28, dissolved in 7 ml of MeOH was treated with 48 mg of palladium on charcoal (10%) and then hydrogenated at RT for 1.5 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, washed with water, and the solution was concentrated in vacuo. The residue was triturated with n hexane / diethyl ether, the solid obtained was filtered off by suction and dried in a high vacuum to give 67mg (90%) of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride as an off-white solid. ISP mass spectrum, m/e: 273.3 (M+1 calculated for $C_{16}H_{20}N_2O_2$: 273).

Example 30

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 3-methoxybenzyl chloride there was obtained: (S)-4-(3-ethoxy-pyrrolidin-1-yl)-7-(3-methoxy-benzyloxy)-2-methyl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 393.3 (M+1 calculated for $C_{24}H_{28}N_2O_3$: 393).

Example 31

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 4-bromomethyl benzonitrile there was obtained: (S)-4-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a yellow solid. ISP mass spectrum, m/e: 388.3 (M+1 calculated for $C_{24}H_{25}N_3O_2$: 388).

Example 32

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 2-bromomethyl benzonitrile there was obtained: (S)-2-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light-orange solid. ISP mass spectrum, m/e: 388.3 (M+1 calculated for $C_{24}H_{25}N_3O_2$: 388).

Example 33

a) A solution of 1g (3.07 mmol) of 7-benzyloxy-6-butyl-4-chloro-quinoline hydrochloride in 2.5 ml (30.7 mmol) of pyrrolidine was heated at 60°C with stirring under an argon atmosphere for 24 h after which time the reaction was completed according to HPLC analysis. The excess pyrrolidine was evaporated off, and the residue was partitioned between EtOAc and water. The layers were separated and the aqueous layer once extracted with AcOEt. The combined organic layers were washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo to give 1.12 g (97.4 %) of the 7-benzyloxy-6-butyl-4-pyrrolidin-1-yl-quinoline as a brown oil. ISP mass spectrum, m/e: 361.3 (M+1 calculated for $C_{24}H_{28}N_2O$: 361).

Preparation of the starting material:

b) A suspension of 1.75 g (5 mmol) of 7-benzyloxy-6-butyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (prepared from methyl benzoquate on ester hydrolysis with KOH in EtOH-H_2O) in 9 ml of quinoline was treated with 57 mg (0.9 mmol) of Cu powder and heated for 1 h at 200 °C. The black reaction mixture was cooled to RT, 80 ml of diethyl ether were added and the solid which precipitated was filtered off by suction. It was then taken up in 100 ml of MeOH, heated to reflux and filtered hot. The filtrate was then concentrated in vacuo. The residue was triturated with diethyl ether, filtered off by suction and dried in a high vacuum to give 966 mg (63 %) of the 7-benzyloxy-6-butyl-1H-quinolin-4-one as a light-yellow solid. ISP mass spectrum, m/e: 308.3 (M+1 calculated for $C_{20}H_{21}NO_2$: 308).

c) A suspension of 900 mg (2.93 mmol) of 7-benzyloxy-6-butyl-1H-quinolin-4-one in 1.44 ml of $POCl_3$ (15.8 mmol) was treated with 0.074 ml of N,N-dimethylaniline and heated at 60°C for 3 h with stirring. The reaction mixture was then poured into ice water and stirred for 0.5 h. The solid which precipitated was filtered off by suction washed with water and dried in a high vacuum to give 1.05 g (99%) of 7-benzyloxy-6-butyl-4-chloro-quinoline hydrochloride as light gray solid. ISP mass spectrum, m/e: XX (M+1 calculated for $C_{20}H_{20}ClNO$: 325.84).

Example 34

A solution of 1.02 g (2.83 mmol) of the 7-benzyloxy-6-butyl-4-pyrrolidin-1-yl-quinoline, product of example 33, dissolved in 50 ml of MeOH was treated with 0.33 g of palladium on charcoal (10%) and then hydrogenated at RT for 2h until TLC analysis indicated the completion of the reaction. The catalyst was filtered off, the solution was concentrated in vacuo and the residue was dried in a high vacuum to give 0.65 g (82 %) of the 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol as a light yellow solid. ISP mass spectrum, m/e: 271.3 (M+1 calculated for $C_{17}H_{22}N_2O$: 271).

Example 35

In analogy to example 6, on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, with methyl iodide chloride there was obtained 6-butyl-7-methoxy-4-pyrrolidin-1-yl-quinoline hydrochloride as a waxy brown solid. ISP mass spectrum, m/e: 285.3 (M+1 calculated for $C_{18}H_{24}N_2O$: 285).

Example 36

In analogy to example 6, on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, with ethyl iodide chloride there was obtained 6-butyl-7-ethoxy-4-pyrrolidin-1-yl-quinoline hydrochloride as an amorphous yellow solid. ISP mass spectrum, m/e: 299.4 (M+1 calculated for $C_{19}H_{26}N_2O$: 299).

Example 37

In analogy to example 6, on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, with bromomethyl cyclopropane there was obtained 6-butyl-7-cyclopropylmethoxy-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 325.3 (M+1 calculated for $C_{21}H_{28}N_2O$: 325).

Example 38

In analogy to example 6, on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, 4-bromomethyl benzonitrile there was obtained 4-(6-butyl-4-pyrrolidin-1-

yl-quinolin-7-yloxymethyl)-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 386.4 (M+1 calculated for $C_{25}H_{27}N_3O$: 386).

Example 39

a) A solution of 2 g (6.9 mmol) of 7-benzyloxy-4-chloro-2-methyl-quinoline, product of example 1d), in 15.5 ml (0.137 mol) of hexamethyleneimine was heated at 120 °C (oil bath temperature) with stirring under an argon atmosphere for 100 h after which time the reaction was completed according to HPLC analysis. The reaction mixture was cooled to RT and then partitioned between EtOAc and water. The layers were separated, the aqueous layer once extracted with AcOEt. The combined organic layers were washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The oily residue was dissolved in a small amount of MeOH and treated under stirring with 4 ml of 3N HCl in MeOH. The solvent was removed in vacuo, the residue triturated with diethyl ether under stirring for 1.5 h and the obtained solid filtered off by suction and dried in a high vacuum. (Further material was obtained on evaporation of the filtrate and treatment of the residue as described above). The desired 4-azepan-1-yl-7-benzyloxy-2-methyl-quinoline hydrochloride, 1.46 g (55.2 %) was thus obtained as a light brown solid. ISP mass spectrum, m/e: 347.4 (M+1 calculated for $C_{23}H_{26}N_2O$: 347).

Example 40

A solution of 1.45 g (3.78 mmol) of 4-azepan-1-yl-7-benzyloxy-2-methyl-quinoline hydrochloride, product of example 39, dissolved in 120 ml of MeOH was treated with 700 mg of palladium on charcoal (10%) and then hydrogenated at RT for 2 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, washed with water, and the solution was concentrated in vacuo. The residue was triturated with diethyl ether, the solid obtained was filtered off by suction and dried in a high vacuum to give 1 g (90.4 %) 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride as a light gray solid. ISP mass spectrum, m/e: 257.2 (M+1 calculated for $C_{16}H_{20}N_2O$: 257).

Example 41

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 4-(chloromethyl)pyridine hydrochloride there

was obtained: 4-azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 348.4 (M+1 calculated for $C_{22}H_{25}N_3O$: 348).

Example 42

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 4-bromomethyl benzonitrile there was obtained: 4-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 372.3 (M+1 calculated for $C_{24}H_{25}N_3O$: 373).

Example 43

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 3-bromomethyl benzonitrile there was obtained: 3-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 372.3 (M+1 calculated for $C_{24}H_{25}N_3O$: 373).

Example 44

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 2-(chloromethyl)pyridine hydrochloride there was obtained: 4-azepan-1-yl-2-methyl-7-(pyridin-2-ylmethoxy)-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 348.5 (M+1 calculated for $C_{22}H_{25}N_3O$: 348).

Example 45

a) A suspension of 1 g (3.5 mmol) of 6-bromo-4-chloro-7-methoxy-2-methyl-quinoline in 20 ml of EtOH was treated sequentially at RT and under stirring with 0.49 g (7 mmol) of pyrrolidine, 0.137 g (1.4 mmol) of pyridine and a catalytic amount of NaI. The mixture was then heated to reflux for 20 h, cooled to RT and concentrated in vacuo. The residue

was applied to a silica gel column with CH_2Cl_2/MeOH (7:1) as eluent. Combinations of the purified fractions and concentration in vacuo gave 0.85 g (68.2%) of the 6-bromo-7-methoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as light brown solid. ISP mass spectrum, m/e: 323.3 (M+1 calculated for $C_{15}H_{17}BrN_2O$: 323).

Preparation of the starting material:

b) 7.66 g (37.9 mmol) of 4-bromo-3-methoxy-phenylamine (preparation described in Tetrahedron Lett., 1995, 7583) were dissolved in 80 ml of cyclohexane at 70°C and subsequently treated under stirring with 72 mg (0.38 mmol) of p-toluenesulfonic acid monohydrate and 4.93 g (37.9 mmol) of ethyl acetoacetate. The solution was then heated at reflux for 3.5 h with a water separator funnel connected. It was then cooled to RT and concentrated in vacuo. The residue was applied to a silica gel column with hexane/diethyl ether (3:1) as eluent. Combinations of the purified fractions and concentration in vacuo gave 8.2 g (68.8%) of the (Z)-3-(4-bromo-3-methoxy-phenylamino)-but-2-enoic acid ethyl ester, as a yellow solid. ISP mass spectrum, m/e: 316.2(M+1 calculated for $C_{13}H_{16}BrNO_3$: 316).

c) A suspension of 6.6 g (21 mmol) of (Z)-3-(4-bromo-3-methoxy-phenylamino)-but-2-enoic acid ethyl ester in 40 ml of Dowtherm A were heated under stirring at 220 °C for 7.5 h after which time TLC analysis indicated completion of the reaction. The mixture was cooled to RT under stirring and the solvent was decanted off. The remaining solid residue was triturated with hexane, filtered off by suction and dried in a high vacuum to give 4.7 g (84%) of the 6-bromo-7-methoxy-2-methyl-quinolin-4-ol as a dark brown solid. EI mass spectrum, m/e: 269 (M calculated for $C_{11}H_{10}BrNO_2$: 269).

d) A suspension of 4.6 g (17.5 mmol) of 6-bromo-7-methoxy-2-methyl-quinolin-4-ol in 14.8 ml (158 mmol) of $POCl_3$ was heated at 60°C for 20 h with stirring. It was then cooled to RT and 50 ml of diethyl ether were added. The solid that precipitated was filtered off by suction and dried in a high vacuum to give 3.85 g of the 6-bromo-4-chloro-7-methoxy-2-methyl-quinoline as a dark brown solid. EI mass spectrum, m/e: 287 (M calculated for $C_{11}H_9BrClNO$: 287).

Example 46

A solution of 115 mg (0.32 mmol) of 6-bromo-7-methoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride, compound of example 45 a), was dissolved in 5 ml of dry CH_2Cl_2 under an argon atmosphere and treated dropwise with 0.16 g (0.64 mmol) of 1M BBr_3 in CH_2Cl_2 with ice cooling. After 0.5 h the ice bath was removed, the solution was stirred for 2 h at RT and then heated to reflux for 12 h. The reaction mixture was cooled to RT and partitioned between ice water and CH_2Cl_2. The layers were separated, the aqueous layer further extracted with CHCl2/MeOH mixtures (8:1).

The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. The residue was applied to a silica gel column with CH_2Cl_2/MeOH (15:1) as eluent. Combinations of the purified fractions and concentration in vacuo gave 39 mg (35%) of the 6-bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol hydrochloride as a light brown solid, ISP mass spectrum, m/e: 307.2 (M+1 calculated for $C_{14}H_{15}BrN_2O$: 307).

Example 47

In analogy to example 6, on reaction 6-bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol hydrochloride, product of example 46, with 4-bromomethyl benzonitrile there was obtained 4-(6-bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 424.3 (M+1 calculated for $C_{22}H_{20}BrN_3O$: 424).

Example 48

a) A solution of 319 mg (0.92 mmol) of 4-chloro-7-methoxy-quinolin-2-ylamine in 20 ml of isopropanol was treated with 130 mg (1.83 mmol) of pyrrolidine and heated at 60°C for 6 h. The reaction mixture was cooled to RT, concentrated in vacuo. The residue was applied to a silica gel column with hexane/AcOEt (1:1) as eluent. The purified fractions were combined and concentrated in vacuo upon which the desired product crystallized out. The crystals were filtered off and dried in a high vacuum to give 48 mg (21%) of 7-methoxy-4-pyrrolidin-1-yl-quinolin-2-ylamine hydrochloride as a light brown solid. EI mass spectrum, m/e: 243.2 (M calculated for $C_{14}H_{17}N_3O$: 243).

b) Above used starting material was obtained from commercially available 1-(4-chloro-7-methoxy-2-quinolyl)-3-phenylurea (500 mg, 1.53 mmol) on heating in a solution of

isopropanol/THF/CH_2Cl_2 (30 ml: 20 ml: 20 ml) and in the presence of 217 mg (3 mmol) of pyrrolidine for 12 h at 60°C. Upon concentration of the reaction mixture the desired product crystallized out. It was filtered off by suction and dried in a high vacuum to give 250 mg (78%) of the 4-chloro-7-methoxy-quinolin-2-ylamine as a light brown solid. ISP mass spectrum, m/e: 208.1 (M calculated for $C_{10}H_9ClN_2O$: 208).

Example 49

In analogy to example 45 a), from 4-chloro-7-methoxyquinoline (synthesis described in: J. Med. Chem., 1998, 4918) and pyrrolidine there was obtained: 7-methoxy-4-pyrrolidin-1-yl-quinoline hydrochloride as a yellow solid. ISP mass spectrum, m/e: 229.2 (M+1 calculated for $C_{14}H_{16}N_2O$: 229).

Example 50

In analogy to example 46, from 7-methoxy-4-pyrrolidin-1-yl-quinoline hydrochloride and on treatment with BBr_3 in toluene under reflux there was obtained was obtained: 4-pyrrolidin-1-yl-quinolin-7-ol as a brown solid. ISP mass spectrum, m/e: 215.3 (M+1 calculated for $C_{13}H_{14}N_2O$: 215).

Example 51

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3,5-dimethoxybenzyl chloride, 7-(3,5-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 379.4 (M+1 calculated for $C_{23}H_{26}N_2O_3$: 379).

Example 52

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3,4-dimethoxybenzyl chloride, whereby the product was isolated as free base, 7-(3,4-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline as a light yellow solid. ISP mass spectrum, m/e: 379.4 (M+1 calculated for $C_{23}H_{26}N_2O_3$: 379).

Example 53

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with ethyl iodide, whereby the product was isolated as free base, 7-ethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline as a brown solid. ISP mass spectrum, m/e: 257.1 (M+1 calculated for $C_{16}H_{20}N_2O$: 257).

Example 54

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 6-methyl-2-chloromethyl-pyridine, 2-Methyl-7-(6-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as off-white solid. ISP mass spectrum, m/e: 334.3 (M+1 calculated for $C_{21}H_{23}N_3O$: 334).

Example 55

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-methyl-3-chloromethyl-pyridine, 2-methyl-7-(2-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as light yellow solid. ISP mass spectrum, m/e: 334.3 (M+1 calculated for $C_{21}H_{23}N_3O$: 334).

Example 56

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 6-chloro-3-chloromethyl-pyridine, 7-(6-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 354.2 (M+1 calculated for $C_{20}H_{20}ClN_3O$: 354).

Example 57

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-chloro-3-chloromethyl-pyridine, 7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 354.3 (M+1 calculated for $C_{20}H_{20}ClN_3O$: 354).

Example 58

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-chloromethyl-2-fluoro-pyridine, 7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 338.2 (M+1 calculated for $C_{20}H_{20}FN_3O$: 338).

Example 59

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-chloro-3-chloromethyl-6-methyl-pyridine, 7-(2-chloro-6-methyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as light yellow solid. ISP mass spectrum, m/e: 368.2 (M+1 calculated for $C_{21}H_{22}ClN_3O$: 368).

Example 60

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-bromomethyl-2-chloro-6-trifluoromethyl-pyridine, whereby the product was isolated as free base, 7-(2-chloro-6-trifluoromethyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline as a white solid. ISP mass spectrum, m/e: 422.2 (M+1 calculated for $C_{21}H_{19}ClF_3N_3O$: 422).

Example 61

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 5-chloromethyl-pyridine-2-carbonitrile, 5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-pyridine-2-carbonitrile hydrochloride as light yellow solid. ISP mass spectrum, m/e: 345.4 (M+1 calculated for $C_{21}H_{20}N_4O$: 345).

Example 62

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-chloro-5-chloromethyl-thiophene, 7-(5-chloro-thiophen-2-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 359.2 (M+1 calculated for $C_{19}H_{19}ClN_2OS$: 359).

Example 63

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-chloromethyl-thiophene, 2-methyl-4-pyrrolidin-1-yl-7-(thiophen-3-ylmethoxy)-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 325.4 (M+1 calculated for $C_{19}H_{20}N_2OS$: 325).

Example 64

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-bromobenzonitrile, whereby the product was isolated as free base, 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-benzonitrile as a white solid. ISP mass spectrum, m/e 330.5 (M+1 calculated for $C_{21}H_{19}N_3O$: 330).

Example 65

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 3-chloromethyl-2-fluoro-pyridine hydrochloride there was obtained: (S) 4-(3-ethoxy-pyrrolidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 382.4 (M+1 calculated for $C_{22}H_{24}FN_3O_2$: 382).

Example 66

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 2-chloro-3-chloromethyl-pyridine hydrochloride there was obtained: (S) 7-(2-chloro-pyridin-3-ylmethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 398.4 (M+1 calculated for $C_{22}H_{24}ClN_3O_2$: 398).

Example 67

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 3-chloromethyl-pyridine

hydrochloride there was obtained: (S) 4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-7-(pyridin-3-ylmethoxy)-quinoline hydrochloride as a light brown solid. ISP mass spectrum, m/e: 364.3 (M+1 calculated for $C_{22}H_{25}N_3O_2$: 364).

Example 68

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 5-chloromethyl-pyridine-2-carbonitrile there was obtained: (S) 5-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile hydrochloride as an off-white solid. ISP mass spectrum, m/e: 389.3 (M+1 calculated for $C_{23}H_{24}N_4O_2$: 389).

Example 69

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 3-methoxybenzyl chloride there was obtained: 4-azepan-1-yl-7-(3-methoxy-benzyloxy)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 377.4 (M+1 calculated for $C_{24}H_{28}N_2O_2$: 377).

Example 70

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 2-bromomethyl-benzonitrile there was obtained: 2-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as an off-white solid. ISP mass spectrum, m/e: 372.3 (M+1 calculated for $C_{24}H_{25}N_3O$: 372).

Example 71

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 3-chlorobenzyl chloride there was obtained: 4-azepan-1-yl-7-(3-chloro-benzyloxy)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 381.3 (M+1 calculated for $C_{23}H_{25}ClN_2O$: 381).

Example 72

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 4-chlorobenzyl chloride there was obtained: 4-Azepan-1-yl-7-(4-chloro-benzyloxy)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 381.3 (M+1 calculated for $C_{23}H_{25}ClN_2O$: 381).

Example 73

A suspension of 98.5 mg (0.25 mmol) of 7-(6-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride, product of example 56, in 0.44 ml (5 mmol) of morpholine was heated under nitrogen at 60°C (oil bath temperature) for 23 h and further 72 h at 100°C. The mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was separated, washed with water, dried over magnesium acetate and concentrated in vacuo. The residue was taken up in ether (20 ml), insoluble material was removed by filtration and the filtrate treated with 0.1 ml of 3 N HCl in MeOH. The solid that precipitated was collected, triturated with ether (5 ml), filtered off by suction, dried in a high vacuum and then applied to a to silica gel column with CH_2Cl_2/MeOH/NH_4OH (19:1: 0.05) as eluent. The purified fractions were combined and concentrated in vacuo to a small volume then acidified by adding a few drops of 3 N HCl in MeOH. The solvent was taken off in vacuo to give 23 mg (18%) of the desired 2-methyl-7-(6-morpholin-4-yl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 405.5 (M+1 calculated for $C_{24}H_{28}N_4O_2$: 405).

Example 74

A suspension of 98.5 mg (0.25 mmol) of 7-(6-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride, product of example 56, 16 mg (0.03 mmol) of BINAP, 2.8 mg (0.01 mmol) of Pd(II) acetate, and 99 mg (1 mmol) of sodium tert-butylate in toluene (4.5 ml) was treated at RT with 36 mg (0.5 mmol) of pyrrolidine and then heated at reflux under an argon atmosphere for 4 h. The reaction mixture was cooled to RT, diluted with methylene chloride (10 ml), and then filtered. The filtrate was concentrated in vacuo, the residue triturated with ether, filtered off by suction and dried in a high vacuum to give 88 mg (84%) of the 2-methyl-4-pyrrolidin-1-yl-7-(6-pyrrolidin-1-yl-pyridin-3-ylmethoxy)-quinoline as a white solid. ISP mass spectrum, m/e: 389.3 (M+1 calculated for $C_{24}H_{28}N_4O$: 389).

Example 75

A suspension of 114 mg (0.5 mmol) of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, 71 mg (0.53 mmol) of 3-dimethylamino-2,2-dimethyl-1-propanol, 196.7 mg (0.75 mmol) of triphenyl phosphine in THF (4 ml) was treated at RT with 123 µl (0.75 mmol) of diethyl azodicarboxylate and stirred at RT for 48 h. The precipitate that had formed was removed by filtration, the filtrate was concentrated in vacuo and the oily residue obtained was applied to silica gel column with CH_2Cl_2/MeOH/NH_4OH (90:10: 1) as eluent. The purified fractions were combined and concentrated in vacuo. The residue was taken up in ether, the crystalline solid that formed was filtered off by suction and dried in a high vacuum to give 24 mg (23%) of the desired [2,2-dimethyl-3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-propyl]-dimethyl-amine as an off-white solid. ISP mass spectrum, m/e: 342.4 (M+1 calculated for $C_{21}H_{31}N_3O$: 342). (Further material, 30 mg, 29%, was obtained on concentration of the mother liquid and collection of the product as hydrochloride salt).

Example 76

In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with 4-hydroxy-1-methylpiperidine there was obtained: 2-methyl-7-(1-methyl-piperidin-4-yloxy)-4-pyrrolidin-1-yl-quinoline as a yellow solid. ISP mass spectrum, m/e: 326.5 (M+1 calculated for $C_{20}H_{27}N_3O$: 326).

Example 77

In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with 3-hydroxy-tetrahydrofurane there was obtained: 2-methyl-4-pyrrolidin-1-yl-7-(tetrahydro-furan-3-yloxy)-quinoline as a light yellow solid. ISP mass spectrum, m/e: 299.4 (M+1 calculated for $C_{18}H_{22}N_2O_2$: 299).

Example 78

In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with (1-methyl-piperidin-4-yl)-methanol, and on isolation of the product as hydrochloride,

there was obtained: 2-Methyl-7-(1-methyl-piperidin-4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 340.3 (M+1 calculated for $C_{21}H_{29}N_3O$: 340).

Example 79

In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with 3-morpholin-4-yl-propan-1-ol, and on isolation of the product as hydrochloride, there was obtained: 2-methyl-7-(3-morpholin-4-yl-propoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 356.4 (M+1 calculated for $C_{21}H_{29}N_3O_2$: 356).

Example 80

To a cooled (0°C) solution of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol (797 mg, 3.49 mmol) in dimethylformamide (13 mL) was added sodium hydride (ca. 60% in oil, 168 mg, 4.19 mmol). After 30 min at 0°C, ethyl bromoacetate (0.5 mL, 4.50 mmol) was injected. After 2h30, an aqueous solution of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine and water and then dried over sodium sulfate. After filtration, solvents were removed in a high vacuum. The brown oil was triturated with diethylether. After filtration, the solid was dried in a high vacuum to give 660 g (60.2 %) of (2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-acetic acid ethyl ester as a light brown solid. ISP mass spectrum, m/e: 315.4 (M+1 calculated for $C_{18}H_{22}N_2O_3$: 315.4).

Example 81

To a cooled (0°C) solution of (2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-acetic acid ethyl ester (613 mg, 1.95 mmol) in ethyl alcohol (10 mL) was added sodium borohydride (506 mg, 12.84 mmol). The mixture was stirred 7h at room temperature. Aqueous hydrochloride was added carefully (12M; 1 mL). The suspension was filtered and the solid was washed with MeOH. The solution was dried over sodium sulfate, filtered and the solvent was removed in a high vacuum to give 425 mg (80.0 %) of 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethanol as a brown oil. ISP mass spectrum, m/e: 273.4 (M+1 calculated for $C_{16}H_{20}N_2O_2$: 273.4).

Example 82

To a cooled (0°C) solution of of 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethanol (425 mg, 1.56 mmol) in dichloromethane (20 mL) was added triethylamine (0.9 mL, 6.49 mmol) and tosyl chloride (1115 mg, 5.85 mmol). The reaction mixture was stirred 22 h at room temperature. An aqueous solution of $NaHCO_3$ was added. After separation, the organic layer was washed with brine. The brown gum was triturated with diethylether. After filtration, the solid was dried in a high vacuum to give 520 mg (78.1 %) of toluene-4-sulfonic acid 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethyl ester as a light yellow solid. ISP mass spectrum, m/e: 427.5 (M+1 calculated for $C_{23}H_{26}N_2O_4S$: 427.5).

Example 83

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 1-(2-pyridyl)-3-chloropropane, there was obtained: 2-methyl-7-(3-pyridin-2-yl-propoxy)-4-pyrrolidin-1-yl-quinoline as a yellow viscous oil. ISP mass spectrum, m/e 348.5 (M+1 calculated for $C_{22}H_{25}N_3O$: 348.5).

Example 84

In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline with morpholine, there was obtained: 7-benzyloxy-2-methyl-4-morpholin-4-yl-quinoline as a waxy yellow solid. ISP mass spectrum, m/e: 335.3 (M+1 calculated for $C_{21}H_{22}N_2O_2$: 335).

Example 85

In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (S)-3-hydroxypyrrolidine (2,5 mole-equivalents) in 1-methyl-2-pyrrolidone as solvent at 100°C, there was obtained: (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol as a light brown solid. ISP mass spectrum, m/e: 335.4 (M+1 calculated for $C_{21}H_{22}N_2O_2$: 335).

Example 86

In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (R)-3-hydroxypyrrolidine (2,5 mole-equivalents) in 1-methyl-2-pyrrolidone as solvent at 100°C, there was obtained: (R)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol as a light brown solid. ISP mass spectrum, m/e: 335.3 (M+1 calculated for $C_{21}H_{22}N_2O_2$: 335).

Example 87

In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (S)-2-(hydroxymethyl)pyrrolidine (2,5 mole-equivalents) in 1-methyl-2-pyrrolidone as solvent at 100°C, there was obtained: (S)-[1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol as an off-white solid. ISP mass spectrum, m/e: 349.5 (M+1 calculated for $C_{22}H_{24}N_2O_2$: 349).

Example 88

In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (S)-2-(methoxymethyl)pyrrolidine (2,5 mole-equivalents) in 1-methyl-2-pyrrolidone as solvent at 100°C, there was obtained: (S)-7-benzyloxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline as an orange viscous oil. ISP mass spectrum, m/e: 363.2 (M+1 calculated for $C_{23}H_{26}N_2O_2$: 363).

Example 89

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline, product of example 88, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 273.2 (M+1 calculated for $C_{16}H_{20}N_2O_2$: 273).

Example 90

In analogy to example 6, on reaction of (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 89, with 2-chloro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-

methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 398.4 (M+1 calculated for $C_{22}H_{24}ClN_3O_2$: 398).

Example 91

In analogy to example 6, on reaction of (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 89, with 2-fluoro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)-7-(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 382.4 (M+1 calculated for $C_{22}H_{24}FN_3O_2$: 382).

Example 92

In analogy to example 6, on reaction of (S)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 89, with cyclopropylmethyl bromide hydrochloride there was obtained: (S)- 7-cyclopropylmethoxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 327.4 (M+1 calculated for $C_{22}H_{26}N_2O_2$: 327).

Example 93

In analogy to example 2, on hydrogenation of (S)-[1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol, product of example 87, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 259.3 (M+1 calculated for $C_{15}H_{18}N_2O_2$: 259).

Example 94

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 2-fluoro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)- {1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol as a light yellow solid. ISP mass spectrum, m/e: 368.4 (M+1 calculated for $C_{21}H_{22}FN_3O_2$: 368).

Example 95

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 2-chloro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)-{1-[7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol as a light yellow solid. ISP mass spectrum, m/e: 384.3 M+1 calculated for $C_{21}H_{22}ClN_3O_2$: 384).

Example 96

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 2-bromomethyl-benzonitrile there was obtained: (S)-2-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as an off-white solid. ISP mass spectrum, m/e: 374.5 (M+1 calculated for $C_{23}H_{23}N_3O_2$: 374).

Example 97

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 3-chlormethyl-pyridine there was obtained: (S)-{1-[2-methyl-7-(pyridin-3-ylmethoxy)-quinolin-4-yl]-pyrrolidin-2-yl}-methanol as an light yellow solid. ISP mass spectrum, m/e: 350.5 (M+1 calculated for $C_{21}H_{23}N_3O_2$: 350).

Example 98

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 5-chloromethyl-pyridin-2-carbonitrile there was obtained: (S)-5-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile as an light yellow solid. ISP mass spectrum, m/e: 375.3 (M+1 calculated for $C_{22}H_{22}N_4O_2$: 375).

Example 99

a) A mixture of 3.1 g of (10.9 mmol) of 7-benzyloxy-4-chloro-6-fluoro-2-methyl-quinoline and 18.1 ml (21.8 mmol) pyrrolidine was heated at 80°C (oil bath temperature) under an argon atmosphere for 6 h. The reaction mixture was concentrated in vacuo, the residue taken up in methylene chloride, which was washed with water, saturated NaCl solution and then dried over magnesium sulphate. The solvent was removed in vacuo, the residue purified by flash chromatography on silica gel with CH_2Cl_2/MeOH (100:0 to 90:10 over 1 h) as eluent. Combination of the purified fractions and concentration in vacuo gave 1.7 g (46.2%) of the 7-benzyloxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline as a brown crystalline solid. ISP mass spectrum, m/e: 337.4 (M+1 calculated for $C_{21}H_{21}FN_2O$: 337).

Preparation of the starting material:

b) A solution of 50 g (0.354 mol) of 4-fluoro-3-methoxy-aniline dissolved in methylene chloride (1800 ml) was treated under argon with 163.2 g (0.44 mol) of tetrabutyl-ammonium iodide, cooled to -75°C and the treated over a period of 25 minutes with 860 ml of 1 M BCl_3 in methylene chloride while keeping the reaction solution between -75°C and -64°C. The solution was stirred for 15 minutes the cooling bath was removed and stirring was continued for 24 h under argon. The reaction solution was poured into ice water (6 l) with stirring, the layers were separated, the water layer twice extracted with mehylene chloride (each 1.5 l). The combined organic layers were washed twice with water (each 2 l) and discarded. The combined aqueous layers were made basic with solid $NaHCO_3$, saturated with NaCl, extracted 3 times with 2.5 l of ether and twice with 1.5 l of AcOEt. The combined organic layers were tried over magnesium sulphate and concentrated in vacuo to give 43.9 g (87.8%) of 4-fluoro-3-hydroxy-aniline as light brown crystalline solid. Melting point: 156-157°C.

c) 79 g (0.62 mol) of 4-fluoro-3-hydroxy-aniline in DMF (1.3 l) were treated under argon portionwise over a period of 15 minutes with 76.7 g (0.68 mol) of potassium t-butylate whereas the temperature of the reaction solution was kept between RT and 28°C. Stirring was continued for 15 minutes then 79 ml (0.68 mol) of benzyl chloride were added dropwise while keeping the temperature of the reaction solution between RT and 30°C. After stirring for 2 h at RT the reaction solution was poured into ice water (6 l) which was then extracted 3-fold with ether (about 3 l each). The combined organic layers were washed with brine (1.5 l) and dried over magnesium sulfate and the solvent removed in vacuo. The residue was purified by chromatography over a short silica gel column with

methylene chloride as eluent. Combination of the purified fractions and concentration in vacuo gave 92.7 g (68.6%) of the desired 3-benzyloxy-4-fluoro-phenylamine as light yellow crystalline solid. ISP mass spectrum, m/e: 218.2 (M+1 calculated for $C_{13}H_{12}FNO$: 218.2).

c) 92.7 g (0.43 mol) of 3-Benzyloxy-4-fluoro-phenylamine, 57 ml (0.45 mol) of ethyl acetoacetate and 0.81 g (4 mmol) of p-toluenesulfonic acid monohydrate in 370 ml of cyclohexane were heated at reflux for 3 h in the presence of a water separator funnel. The reaction mixture was cooled to RT, ACOEt (1 l) and saturated aqueous $NaHCO_3$ solution (0,5 l) were added, the layers were separated and the organic layer once extracted with AcOEt (0.3 l). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give 140 g (100%) of the desired 3-(3-benzyloxy-4-fluoro-phenylamino)-but-2-enoic acid ethyl ester as yellow-orange crystalline solid. Melting point: 79°C-80°C.

d) 70.35 g (0.21 mol) of 3-(3-benzyloxy-4-fluoro-phenylamino)-but-2-enoic acid ethyl ester in Dowtherm A (220 ml) were added dropwise under argon to 400 ml of Dowtherm A heated at 250°C (metal bath temperature). The solution was stirred further 15 minutes at 250°C (bath temperature), cooled to RT and n-hexane was added with stirring whereby a light brown solid formed that was collected by filtration and washed with 4-times with n-hexane. The solid was then triturated with ether, collected by suction, washed 3-times with ether and then dried in a high vacuum, to give 33.9 g (57%) of the desired7-benzyloxy-6-fluoro-2-methyl-1H-quinolin-4-one as a light brown solid. ISP mass spectrum, m/e: 284.1 (M+1 calculated for $C_{17}H_{14}FNO_2$: 284).

e) 67.8 g (0.239 mol) of 7-benzyloxy-6-fluoro-2-methyl-1H-quinolin-4-one in 220ml (2.39 mol) of $POCl_3$ were heated at reflux for 90 minutes. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was partitioned between ice water (1.5 l) and methylene chloride (1 l), and 250 ml of concentrated ammonia were added slowly with stirring to adjust the aqueous layer to pH9. The layers were separated, the aqueous layer twice extracted with methylene chloride (each 500 ml), the combined organic layers were washed with brine, dried over magnesium sulfate and then concentrated in vacuo, to give 71.5 g (86.83%) of the desired of 7-benzyloxy-4-chloro-6-fluoro-2-methyl-quinoline as an off white solid. Melting point: 110°C-111°C.

Example 100

A solution of 1.5 g (4.46 mmol) of 7-benzyloxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline, product of example 99, dissolved in 40 ml of MeOH was treated with 0.375 g of palladium on charcoal (10%) and then hydrogenated at RT for 1.5 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, and the solution was concentrated in vacuo. The residue was triturated with AcOEt, collected by filtration and dried in a high vacuum to give 1.02 g (92.8%) 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol as an yellow solid. ISP mass spectrum, m/e: 247.3 (M+1 calculated for $C_{14}H_{15}FN_2O$: 247).

Example 101

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 4-bromomethyl-benzonitrile whereby the product was isolated as free base, 4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as an off-white solid. ISP mass spectrum, m/e: 362.2(M+1 calculated for $C_{22}H_{20}FN_3O$: 362).

Example 102

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 3-bromomethyl pyridine hydrochloride whereby the product was isolated as free base, 6-fuoro-2-methyl-7-(pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline as an brown solid. ISP mass spectrum, m/e: 338.2(M+1 calculated for $C_{20}H_{20}FN_3O$: 338).

Example 103

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 3-chloromethyl 2-fluoro-pyridine hydrochloride whereby the product was isolated as free base, 6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline as an brown solid. ISP mass spectrum, m/e: 356.4 (M+1 calculated for $C_{20}H_{19}F_2N_3O$: 356).

Example 104

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 2-chloro-3-chloromethyl-pyridine hydrochloride whereby the product was isolated as free base, 7-(2-chloro-pyridin-3-ylmethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline as a light brown solid. ISP mass spectrum, m/e: 372.3 (M+1 calculated for $C_{20}H_{19}ClFN_3O$: 372).

Example 105

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 3-chloromethyl-2-methyl-pyridine hydrochloride whereby the product was isolated as free base, 6-fluoro-2-methyl-7-(2-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline an light yellow solid. ISP mass spectrum, m/e: 352.4(M+1 calculated for $C_{21}H_{22}FN_3O$: 352).

Example 106

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 3-chloromethyl benzonitrile whereby the product was isolated as free base, 3-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as an off-white solid. ISP mass spectrum, m/e: 362.2(M+1 calculated for $C_{22}H_{20}FN_3O$: 362).

Example 107

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 2-bromomethyl benzonitrile whereby the product was isolated as free base, 2-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as light brown solid. ISP mass spectrum, m/e: 362.2(M+1 calculated for $C_{22}H_{20}FN_3O$: 362).

Example 108

In analogy to example 6 there was prepared, on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with cyclopropylmethyl bromide, 7-cyclopropylmethoxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a yellow solid. ISP mass spectrum, m/e: 301.3 (M+1 calculated for $C_{18}H_{21}FN_2O$: 301).

Example 109

In analogy to example 6 there was prepared, on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 5-chloromethyl-pyridine-2-carbonitrile, whereby the product was isolated as free base, 5-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-pyridine-2-carbonitrile as light grey solid. ISP mass spectrum, m/e: 363.2 (M+1 calculated for $C_{21}H_{19}FN_4O$: 363).

Example 110

A suspension of 3.2 g (9.5 mmol) of (R)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 86, in THF (275 ml) was treated at RT under nitrogen with 1.42 g (12.4 mmol) of potassium tert-butoxide. The suspension was stirred for 20 minutes at RT then 0.72 ml (11.4 mmol) of methyl iodide were added. After 25 minutes of stirring further 0.284 g (2.48 mmol) of potassium tert-butoxide were added followed by 0.144 ml (2.28 mol) of methyl iodide (10 minutes later) for completion of the reaction. Stirring was continued for 20 minutes, the reaction mixture was then concentrated in vacuo and the residue partitioned between water and AcOEt. The layers were separated the aqueous layer once extracted with AcOEt, the combined organic layers washed with brine, dried over magnesium sulphate and concentrated in vacuo to give 3.33 g (94.5%) (R)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline as an orange viscous oil. ISP mass spectrum, m/e: 349.5 (M+1 calculated for $C_{22}H_{24}FN_2O2$: 349).

Example 111

In analogy to example 110 there was prepared, on reaction of (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with 2-bromoethylmethyl

ether, (S)-7-benzyloxy-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinoline an orange viscous oil. ISP mass spectrum, m/e: 393.4 (M+1 calculated for $C_{24}H_{28}N_2O_3$: 393).

Example 112

In analogy to example 110 there was prepared: on reaction of (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with methyl iodide, (S)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline as an yellow viscous oil. ISP mass spectrum, m/e: 349.3 (M+1 calculated for $C_{22}H_{24}N_2O_2$: 349).

Example 113

In analogy to example 110 there was prepared: on reaction of (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with cyclopropyl bromide, (S)-7-benzyloxy-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinoline as an orange viscous oil. ISP mass spectrum, m/e: 389.2 (M+1 calculated for $C_{25}H_{28}N_2O_2$: 389).

Example 114

In analogy to example 110 there was prepared: on reaction of (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with toluene-4-sulfonic acid 3-methoxy-propyl ester, (S)-7-benzyloxy-4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinoline as an yellow viscous oil. ISP mass spectrum, m/e: 407.3 (M+1 calculated for $C_{25}H_{30}N_2O_3$: 407).

Example 115

In analogy to example 110 there was prepared: on reaction of (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with 2-(2-bromo-ethoxy)-tetrahydro-pyran, 7-benzyloxy-2-methyl-4-[(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl]-quinoline as an yellow viscous oil. ISP mass spectrum, m/e: 363.4 (M+1 calculated for $C_{28}H_{34}N_2O_4$: 463).

Example 116

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinoline, product of example 111, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 303.4 (M+1 calculated for $C_{17}H_{22}N_2O_3$: 303).

Example 117

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline, product of example 112, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 259.2 (M+1 calculated for $C_{15}H_{18}N_2O_2$: 259).

Example 118

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinoline, product of example 113, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 299.3 (M+1 calculated for $C_{18}H_{22}N_2O_2$: 299).

Example 119

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinoline, product of example 114, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 317 (M+1 calculated for $C_{18}H_{24}N_2O_3$: 317).

Example 120

In analogy to example 2, on hydrogenation of 7-benzyloxy-2-methyl-4-{(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinoline, product of example 115,

with Pd on charcoal (10%) in MeOH, there was obtained: 2-methyl-4-{(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 373.4.3 (M+1 calculated for $C_{21}H_{28}N_2O_4$: 373).

Example 121

In analogy to example 6, on reaction of (S)- 4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol, product of example 116, with 4-bromomethyl benzonitrile there was obtained: (S)- 4-{4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 418.4 (M+1 calculated for $C_{25}H_{27}N_3O_3$: 418.4).

Example 122

In analogy to example 6, on reaction of (S)- 4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 117, with 4-bromomethyl benzonitrile there was obtained: (S)- 4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 374.4 (M+1 calculated for $C_{23}H_{23}N_3O_2$: 374).

Example 123

In analogy to example 6, on reaction of (S)- 4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 118, with 4-bromomethyl benzonitrile there was obtained: (S)-4-[4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as an off-white solid. ISP mass spectrum, m/e: 414.4 (M+1 calculated for $C_{26}H_{27}N_3O_2$: 414).

Example 124

In analogy to example 6, on reaction of (S)- 4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol, product of example 119, with 4-bromomethyl benzonitrile there was obtained: (S)-4-{4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile hydrochloride as an off-white solid. ISP mass spectrum, m/e: 432.5 (M+1 calculated for $C_{26}H_{29}N_3O_3$: 432).

Example 125

In analogy to example 6, on reaction of 2-methyl-4-[(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl]-quinolin-7-ol, product of example 120, with 4-bromomethyl benzonitrile, and subsequent cleavage of the THP ether protecting group whereby the product was isolated as free base, there was obtained: (S)-4-{4-[3-(2-Hydroxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile as a white yellow solid. ISP mass spectrum, m/e: 405.3 (M+1 calculated for $C_{24}H_{25}N_3O_3$: 403).

Example 126

In analogy to example 99, on reaction of 7-benzyloxy-4-chloro-6-fluoro-2-methyl-quinoline, with an excess of (S)-2-(hydroxymethyl)pyrrolidine (2,5 mole-equivalents) in 1-methyl-2-pyrrolidone as solvent at 100°C, there was obtained: (S)-[1-(7-benzyloxy-6-fluoro-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol as an light brown solid. ISP mass spectrum, m/e: 367.3 (M+1 calculated for $C_{22}H_{23}FN_2O_2$: 367).

Example 127

In analogy to example 100, on hydrogenation of (S)-[1-(7-benzyloxy-6-fluoro-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol, product of example 126, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a light brown solid. ISP mass spectrum, m/e: 277.3 (M+1 calculated for $C_{15}H_{17}FN_2O_2$: 277).

Example 128

In analogy to example 6, on reaction of (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 127, with 4-bromomethyl benzonitrile, whereby the product was isolated as free base, there was obtained: (S)-4-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as an light grey solid. ISP mass spectrum, m/e: 392.3 (M+1 calculated for $C_{23}H_{22}FN_3O_2$: 392).

Example 129

In analogy to example 6, on reaction of (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 127, with 5-chloromethyl-pyridine-2-carbonitrile, whereby the product was isolated as free base, there was obtained (S)-5-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile as a grey solid. ISP mass spectrum, m/e: 393.3 (M+1 calculated for $C_{22}H_{21}FN_4O_2$: 393).

Example 130

a) A solution of 1.42 g of (4.6 mmol) of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile and 1.11 g (12.5 mmol) of (S)-3-hydroxypyrrolidine in 1-methyl-2-pyrrolidine (25 ml) was heated under nitrogen at 100°C (oil bath temperature) for 23 h. The reaction mixture was concentrated in a high vacuum, the residue taken up in methylene chloride, which was washed with water, saturated NaCl solution and then dried over magnesium sulphate. The solvent was removed in vacuo, the residue triturated with MeOH, filtered off by suction, washed subsequently with MeOH and ether and then dried in a high vaccum to give 1.45 g (83.86%) of the (S)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a brown solid. ISP mass spectrum, m/e: 360.2 (M+1 calculated for $C_{22}H_{21}N_3O_2$: 360.2).

Preparation of the starting material:

b) A solution of 3 g (10.5 mmol) of 7-benzyloxy-2-methyl-quinolin-4-ol, product of example 1 c), dissolved in 270 ml of MeOH was treated with 1 g of palladium on charcoal (10%) and then hydrogenated at RT for 1 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, washed with MeOH, and the solution was concentrated in vacuo. The residue was triturated with ether, collected by filtration and dried in a high vacuum to give 2.05 g (98.6%) 2-methyl-quinoline-4,7-diol as an off-white solid. ISP mass spectrum, m/e: 176.2 (M+1 calculated for $C_{10}H_9NO_2$: 176).

c) A mixture of 2.05 g (10.4 mmol) of 2-methyl-quinoline-4,7-diol, 1.72 g (12.5 mmol) of potassium carbonate and 2.1 g (12.5 mmol) of 4-(bromomethyl)-benzonitrile in 100ml of DMF were stirred at RT under an nitrogen atmosphere for 4 h until completion of the reaction according to HPLC analysis. The reaction mixture was cooled to RT and poured

into EtOAc / water (300 ml / 400 ml). The product that precipitated was filtered off by suction, washed with water, AcOEt and ether and dried in a high vacuum to give 2.23 g (73%) of 4-(4-hydroxy-2-methyl-quinolin-7-yloxymethyl)-benzonitrile as a white solid. ISP mass spectrum, m/e: 291.4 (M+1 calculated for $C_{18}H_{14}N_2O_2$: 291).

d) 2.22 g (7.6 mmol) of 4-(4-hydroxy-2-methyl-quinolin-7-yloxymethyl)-benzonitrile in 14.2 ml (151.7mmol) of $POCl_3$ were heated at 130°C (oil bath temperature) for 1h 50 min until completion of the reaction according to TLC analysis. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was taken up in ice water and stirred for 15 minutes. The pH was adjusted to values between pH 9-10 with concentrated NH_4OH an stirring was continued for 2h. The brown solid, which precipitated was filtered off by suction, washed with water and subsequently dried in a high vacuum. This gave 2.38 g (100%) of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile as a yellow solid. ISP mass spectrum, m/e: 209 (M+1 calculated for $C_{18}H_{13}ClN2O$: 309).

Example 131

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R)-3-hydroxypyrrolidine, there was obtained (R)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a brown solid. ISP mass spectrum, m/e: 360.3 (M+1 calculated for $C_{21}H_{21}N_3O_2$: 360).

Example 132

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-2-methylpyrrolidine, there was obtained (R,S)-4-[2-methyl-4-(2-methyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile as a beige solid. ISP mass spectrum, m/e: 358.2 (M+1 calculated for $C_{23}H_{23}N_3O$: 358).

Example 133

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (S)-2-(hydroxymethyl)pyrrolidine, there

was obtained: (S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 374.4 (M+1 calculated for $C_{23}H_{23}N_3O_2$: 374).

Example 134

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R)-2-(hydroxymethyl)pyrrolidine, there was obtained: (R)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 374.4 (M+1 calculated for $C_{23}H_{23}N_3O_2$: 374).

Example 135

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R)-3-(dimethylamino)pyrrolidine, there was obtained: (R)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light brown solid. ISP mass spectrum, m/e: 387.3 (M+1 calculated for $C_{24}H_{26}N_4O$: 387).

Example 136

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (S)-3-(dimethylamino)pyrrolidine, there was obtained: (S)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light brown solid. ISP mass spectrum, m/e: 387.3 (M+1 calculated for $C_{24}H_{26}N_4O$: 387).

Example 137

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R)-2-(methoxymethyl)pyrrolidine, there was obtained: (R)-4-[4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light brown solid. ISP mass spectrum, m/e: 388.3 (M+1 calculated for $C_{24}H_{25}N_3O_2$: 388).

Example 138

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (S)-2-(methoxymethyl)pyrrolidine, there was obtained: (S)-4-[4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light brown solid. ISP mass spectrum, m/e: 388.3 (M+1 calculated for $C_{24}H_{25}N_3O_2$: 388).

Example 139

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-2-isopropyl-pyrrolidine, there was obtained: (R,S)-4-[4-(2-isopropyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 386.4 (M+1 calculated for $C_{25}H_{27}N_3O$: 386).

Example 140

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (S)-proline methyl ester, there was obtained: (S)-1-[7-(4-cyano-benzyloxy)-2-methyl-quinolin-4-yl]-pyrrolidine-2-carboxylic acid methyl ester as a white solid. ISP mass spectrum, m/e: 402.5 (M+1 calculated for $C_{24}H_{23}N_3O_3$: 402).

Example 141

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R)-3-(methylamino)pyrrolidine there was obtained: (R)-4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile as a yellow foam. ISP mass spectrum, m/e: 373.4 (M+1 calculated for $C_{23}H_{24}N_4O$: 373).

Example 142

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (S)-3-(methylamino)pyrrolidine there was obtained: (S)- 4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile as a brown foam. ISP mass spectrum, m/e: 373.4 (M+1 calculated for $C_{23}H_{24}N_4O$: 373).

Example 143

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with piperidine there was obtained: 4-(2-methyl-4-piperidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a yellow solid. ISP mass spectrum, m/e: 358.3 (M+1 calculated for $C_{23}H_{23}N_3O$: 358).

Example 144

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with morpholine there was obtained: 4-(2-methyl-4-morpholin-4-yl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 360.3 (M+1 calculated for $C_{22}H_{21}N_3O_2$: 360).

Example 145

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-3-(diethylamino)pyrrolidine there was obtained: (R,S)-4-[4-(3-diethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light brown solid. ISP mass spectrum, m/e: 415.4 (M+1 calculated for $C_{27}H_{31}N_5O$: 415).

Example 146

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-2-(pyrrolidin-3yl)-pyridine there was obtained: (R,S)-4-[2-methyl-4-(3-pyridin-2-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-

benzonitrile hydrochloride as a brown solid. ISP mass spectrum, m/e: 421.4 (M+1 calculated for $C_{27}H_{24}N_4O$: 421).

Example 147

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-4-(pyrrolidin-3-yl)-pyridine there was obtained: (R,S)-4-[2-methyl-4-(3-pyridin-4-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile as a white solid. ISP mass spectrum, m/e: 421.4 (M+1 calculated for $C_{27}H_{24}N_4O$: 421).

Example 148

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (S)-1-(2-pyrrolidinylmethyl)pyrrolidine there was obtained: (S)- 4-[2-methyl-4-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a brown solid. ISP mass spectrum; m/e: 427.6 (M+1 calculated for $C_{27}H_{30}N_4O$: 427).

Example 149

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-3-(methylsulfonyl)-pyrrolidine there was obtained: (R,S)-4-[4-(3-methanesulfonyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light brown solid. ISP mass spectrum, m/e: 422.4 (M+1 calculated for $C_{23}H_{23}N_3O_3S$: 422).

Example 150

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-3-methyl-piperidine there was obtained: (R,S)-4-[2-methyl-4-(3-methyl-piperidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 372.4 (M+1 calculated for $C_{24}H_{25}N_3O$: 372).

Example 151

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with 1,4-dioxa-8-azaspiro{4.5}decane there was obtained: 4-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 416.4 (M+1 calculated for $C_{25}H_{25}N_3O_3$: 416).

Example 152

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-3-(hydroxymethyl)piperidine there was obtained: (R,S)- 4-[4-(3-hydroxymethyl-piperidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 388.3 (M+1 calculated for $C_{24}H_{25}N_3O_2$: 388).

Example A

A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	Per tablet
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

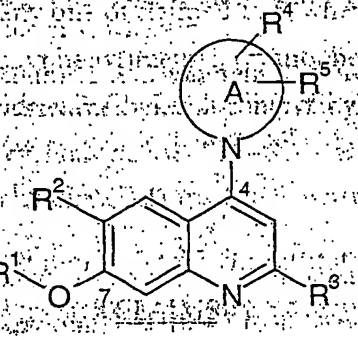
Example B:

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

CLAIMS

1. Compounds of formula I



I

wherein

R^1 is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH_2-SO_2-, monoalkylamino-SO_2-, dialkylamino-SO_2-, alkyl-SO_2-, aryl, NH_2-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, aryl-SO_2-O-alkyl, cycloalkyl or cycloalkylalkyl;

R^2 is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH_2-, monoalkylamino, dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, aryl, arylalkoxy or heteroarylalkoxy;

R^3 is hydrogen, alkyl, NH_2-, monoalkylamino, dialkylamino or alkoxy;

R^4 is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, NH_2-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO_2- or aryl-SO_2-;

R^5 is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, NH_2-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy,

heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO_2- or aryl-SO_2-;

A is a 5- to 10- membered mono- or bicyclic saturated heterocyclic ring comprising the nitrogen atom which is attached to the quinoline ring and optionally one or two further heteroatoms which are independently selected from oxygen, sulfur and nitrogen;

and pharmaceutically acceptable salts and esters thereof.

2. Compounds according to claim 1, wherein

R^1 is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH_2-SO_2-, monoalkylamino-SO_2-, dialkylamino-SO_2- or alkyl-SO_2-;

R^4 is hydrogen, alkyl, alkoxy, hydroxy, NH_2-, monoalkylamino, dialkylamino, acetylamino or cyano;

R^5 is hydrogen; and

A is a saturated ring consisting of a nitrogen atom which is attched to the quinoline ring and a $-(CH_2)_n-$ moiety with n being 4, 5, or 6.

3. Compounds according to claims 1 or 2, wherein R^1 is hydrogen, cycloalkylalkyl, aralkyl, or heteroarylalkyl.

4. Compounds according to any one of claims 1 to 3, wherein R^1 is hydrogen, aralkyl or heteroarylalkyl.

5. Compounds according to any one of claims 1 to 4, wherein R^1 is hydrogen, phenylalkyl or pyridinylalkyl, wherein the phenyl- and the pyridinyl cycles are optionally substituted with one to three substituents independently selected from alkoxy, cyano and halogen.

6. Compounds according to any one of claims 1 to 5, wherein R^1 is hydrogen, cyclopropylmethyl, (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl, pyridinylmethyl, chloropyridinylmethyl or fluoropyridinylmethyl.

7. Compounds according to any one of claims 1 to 6, wherein R^2 is hydrogen, alkyl or halogen.

8. Compounds according to claim 7, wherein R^2 is hydrogen.

9. Compounds according to claim 7, wherein R^2 is alkyl.

10. Compounds according to claim 7, wherein R^2 is hydrogen, butyl, fluoro, chloro or bromo.

11. Compounds according to any one of claims 1 to 10, wherein R^3 is hydrogen, alkyl, or NH_2-.

12. Compounds according to claim 11, wherein R^3 is alkyl.

13. Compounds according to claim 12, wherein R^3 is methyl.

14. Compounds according to any one of claims 1 to 13, wherein R^4 is hydrogen, alkoxy, alkoxyalkyl, hydroxyalkyl or hydroxy.

15. Compounds according to claim 14, wherein R^4 is hydrogen.

16. Compounds according to any one of claims 1 to 15, wherein A is a pyrrolidinyl or azepanyl ring.

17. Compounds according to claim 16, wherein A is a pyrrolidinyl ring.

18. Compounds according to any one of claims 1 to 17, wherein R^5 is hydrogen.

19. Compounds according to any one of claims 1 to 18 selected from

2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol;

7-(3-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

7-(3-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(4-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

(S)-4-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol;

4-(6-butyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

4-azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline;

4-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;

3-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;

7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

(S)-4-(3-ethoxy-pyrrolidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinoline;

(S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;

(S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

(S)-7-(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

(S)-{1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;

(S)-{1-[7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;

4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(2-chloro-pyridin-3-ylmethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;

(S)-4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

(S)-4-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

(S)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

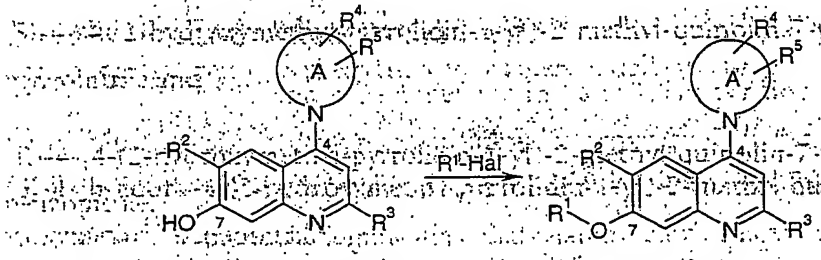
(R)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

(S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile and

(R)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile.

20. A process for the preparation of a compound according to any one of claims 1 to 19 comprising one of the following reactions

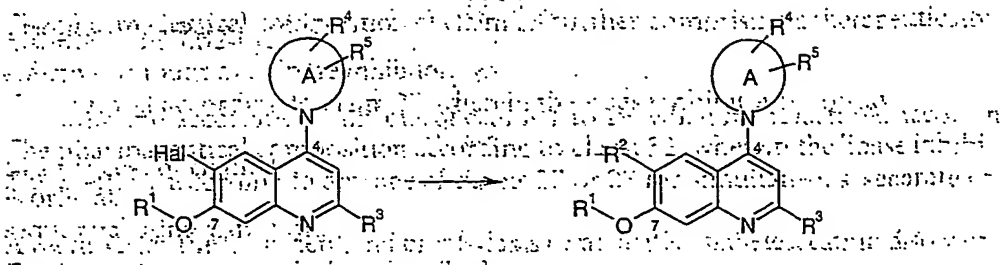
a) reaction of a compound of the formula Ia in the presence of a compound of the formula R^1-Hal



Ia I

wherein R^1, R^2, R^3, R^4, R^5 and A are as defined in claim 1 and Hal is halogen; or

b) a Pd catalyzed C/O, C/N or C/C bond forming reaction of a compound of formula Ic in order to obtain a compound of formula I

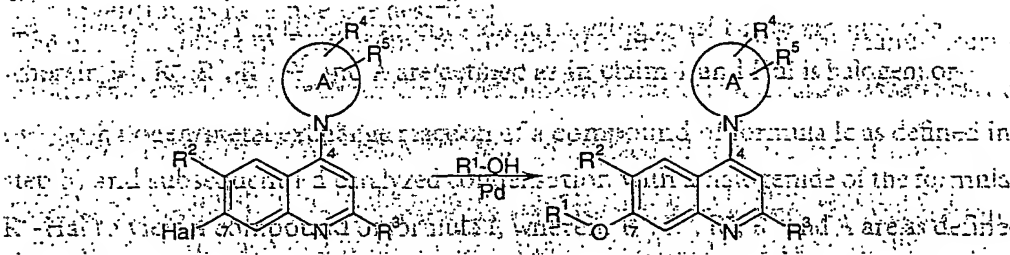


Ic

wherein R^1, R^2, R^3, R^4, R^5 and A are defined as in claim 1 and Hal is halogen; or

c) a halogen/metal exchange reaction of a compound of formula Ic as defined in step b) and subsequent Pd catalyzed condensation with a halogenide of the formula R^2-Hal to yield a compound of formula I, wherein R^1, R^3, R^4, R^5 and A are as defined in claim 1, Hal is halogen and R^2 is alkenyl, alkinyl, alkoxy, alkoxyalkoxy, aryloxy, arylamino, heteroarylamino, NH_2-, monoalkylamino, dialkylamino, arylalkylamino, heteroarylalkylamino, aryl, arylalkoxy or heteroarylalkoxy; or

d) reaction of a compound of formula II in the presence of an alcohol of the formula R^1-OH and a palladium catalyst in order to obtain a compound of formula I



wherein R^2, R^3, R^4, R^5 and A are as defined in claim 1, Hal is halogen and R^1 is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH_2-SO_2-, monoalkylamino-SO_2-, dialkylamino-SO_2-, alkyl-SO_2-, aryl, NH_2-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, aryl-SO_2-O-alkyl, cycloalkyl or cycloalkylalkyl.

21. Compounds according to any one of claims 1 to 19 for use as therapeutically active substance.

22. Compounds according to any one of claims 1 to 19 for the preparation of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the NPY receptor.

23. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 19 and a therapeutically inert carrier.

24. The use of a compound according to any one of claims 1 to 19 for the preparation of medicaments for the treatment and prophylaxis of arthritis, diabetes, eating disorders and obesity.

25. A compound according to any one of claims 1 to 19, when manufactured according to a process of claim 20.

26. A method for the treatment and prophylaxis of arthritis, diabetes, eating disorders and obesity, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 19.

27. A method of treatment of obesity in a human in need of such treatment which comprises administration to the human a therapeutically effective amount of a compound as defined in any one of the claims 1 to 19 and a therapeutically effective amount of a lipase inhibitor.

28. The method according to claim 27, wherein the lipase inhibitor is orlistat.

29. The method according to any one of claims 27 or 28 for simultaneous, separate or sequential administration.

30. The use of a compound according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor.

31. The use according to claim 30, wherein the lipase inhibitor is orlistat.

32. The pharmaceutical composition of claim 23 further comprising a therapeutically effective amount of a lipase inhibitor.

33. The pharmaceutical composition according to claim 32, wherein the lipase inhibitor is orlistat.

34. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/05120

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/42 C07D401/04 C07D401/12 C07D405/12 C07D409/12
A61K31/4706 A61K31/4709 A61P3/04 A61P19/02 A61P3/10
C07D401/14 C07D405/14 C07D491/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 035 367 A (SIMPSON WILLIAM R) 12 July 1977 (1977-07-12) column 1, line 23 -column 2, line 55 column 4, line 4 -column 5, line 5; examples 4G,4H,Z-33,Z-34 --- -/--	1-19, 21-26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2002	02/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CRONIN, TIMOTHY H.; HESS, HANS J. E.: "Hypotensive and bronchodilatory quinolines, isoquinolines, and quinazolines" Database accession no. 70:68419 (DN) XP002209016 RN 21560-24-7, 21560-25-8, 21579-67-9 abstract & ZA 6 706 512 A (PFIZER, CHAS., AND CO., INC.) 3 June 1968 (1968-06-03)	1-19, 21-23,25
X	US 3 272 824 A (FREDERICK EBETINO FRANK ET AL) 13 September 1966 (1966-09-13) column 1, line 39 - line 54; claim 1; examples VII,XIII	1-19, 21-23,25
X	GB 991 838 A (RHONE POULENC SA) 12 May 1965 (1965-05-12) page 4, line 45 - line 49; claims 1,10,11,26; examples V,XX,XXI	1-19,21, 23,25
X	GAUTHIER B ET AL: "RECHERCHE SUR LES AMINOQUINOLEINES. ETUDES CHIMIQUE, ANTIPARASITAIRE, ANTIMICROBIENNE ET ANTIFONGIQUE DE (MONO, DI ET TRICHLORACETYL-4 PIPERAZINYL-1)-4 QUINOLEINES//AMINOQUINOLEIN RESEARCH. CHEMICAL, ANTIPARASITIC, ANTIMICROBIAL AND ANTIFUNGAL STUDY OF (" ANNALES PHARMACEUTIQUES FRANCAISES, MASSON, PARIS, FR, vol. 1, no. 44, 22 August 1986 (1986-08-22), pages 55-64, XP001063055 ISSN: 0003-4509 scheme 1 abstract; tables I-III	1-19,21, 23,25
X	EP 0 882 717 A (KYOWA HAKKO KOGYO KK) 9 December 1998 (1998-12-09) page 9, formula II example 407	1-19
P,X	WO 02 20488 A (HOFFMANN LA ROCHE) 14 March 2002 (2002-03-14) page 8, line 9 - line 10 claims	1-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/05120

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 34
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 34

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "pharmaceutically acceptable esters" (including "physiologically acceptable equivalents" thereof; cf. present description, p. 7, lines 16-23) does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within its scope. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include "pharmaceutically acceptable esters" of the compounds of formula I.

The vague reference in claim 34 to "the invention as hereinbefore described" leaves the reader in doubt as to the scope of said claim (Article 6 PCT). The resulting lack of clarity is such as to preclude a meaningful search of this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

[redacted]TERNATIONAL SEARCH REPORT

Information on patent family members

[redacted]ternational Application No
PCT/EP 02/05120

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			US	2002068734 A1	06-06-2002
			CA	2239227 A1	09-04-1998
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			WO	0220488 A2	14-03-2002
			US	2002052356 A1	02-05-2002